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A SURVEY OF CHILDHOOD MALIGNANCIES

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SECTION I. BACKGROUND TO THE SURVEY

The present survey is based on an earlier study of the vital statistics relating to leukaemia (Hewitt, 1955). This had revealed an unusual peak of mortality in the third and fourth years of life which indicated that the subsequent survey should, in the first instance, be restricted to children. The earlier investigation had also led to the suggestion that it might be particularly worth while to study modern innovations, such as radiology.

Method

An attempt was made to trace all children in England and Wales who had died of leukaemia or cancer before their tenth birthday during the years 1953 to 1955 (case group) and to compare their pre-natal and post-natal experiences with those of healthy children (control group). Details of control selection and method of recording data are given later, but the basic idea was to obtain the necessary facts from the mothers by sending a specially appointed "survey doctor" to interview, first, the mother of a dead child, and, secondly, the mother of a live child matched for age, sex, and locality but otherwise picked at random from the local birth register.

Available Cases.—The total number of deaths in the category required was 1,694, of which 792 were ascribed to leukaemia and 902 to other cancers (Registrar-General, 1954–6). By May, 1957, the mothers of 1,416 of these children had been interviewed (677 leukaemia and 739 other cancers). The lost cases represented 16.4% of the total, and included 6.8% who belonged to families that had moved abroad or to an unknown address and 3.1% where the interview could not be arranged in time. The remainder represented refusals to co-operate, 4.5% by parents and 2.0% by doctors.

Appointment of Survey Doctors.—It was a basic principle of the survey that the same doctor should interview both mothers of a given case/control pair, but that pairs in different local authority areas might be seen by different doctors. The 90 pairs belonging to the London County Council area were seen by one of us (J. W.) and the remaining 1,326 pairs by "survey doctors" appointed by the principal medical officer of health to the areas. All local authorities co-operated, so that all parts of the country are represented in the survey. To ensure uniformity in the recording of data and the selection of controls one of us (A. S.) visited each one of the health departments to give detailed instructions about field-work procedures.

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Collecting of Data

Each survey doctor was given a list of the cases in his area. If the mothers or foster-mothers were still living in the area he was to see them and the corresponding control-mothers: if a mother had left the area he was to find and interview a control, but return the case papers to Oxford. These were eventually sent on to the new area, but in this way a central record was kept of all "transfers." No case/control pairs seen by different doctors have been included in the analyses making direct comparison between cases and controls, but they may feature in other analyses—for example, incidence of mongolism. Since the records obtained from foster-mothers contained no information about the pre-natal environment they too have been excluded from the case/control comparisons.

The questionaries for recording the interviews were the same for cases and controls, and were distributed in pairs bearing the same serial number and a so-called final date. This was the date of death of the case, and was a reminder that the medical history of the control child should cease at the so-called onset date—that is, the date when the corresponding child fell ill. The first half of the questionary described the children's medical experiences before the onset date—that is, illnesses, *x*-ray exposures and antibiotics—their feeding habits, and their exposures to non-medical ionizing radiations (television, luminous toys, and pedoscopes) during this period, The second half described the mother and other relatives. The mother's illness and *x*-ray histories ceased at the date of birth of the survey child, but the family histories continued to the date of the interview (this allowed the total number of children in the family, and the number of relatives dying from cancer, to be the number up to the time of the interview). The mother's illness and *x*-ray histories were recorded separately for three periods of her life: (1) the first period, before marriage; (2) the middle period, between marriage and the relevant conception; and (3) the final period, during the relevant pregnancy. If the child was illegitimate the first period extended to the relevant conception.

Control Selection

It was clear that some "matching" of the live and dead children was needed, but it was decided to restrict this to three features of cancer deaths which it was not intended to study—namely age, sex, and locality. The distribution of the dead children in respect of these three influences could be readily obtained from official mor-

tality statistics, but as yet nothing was known about, for example, their parity or social class distribution.

Accompanying the papers for each case/control pair was a so-called control selection list. On this was entered the name of the dead child, its sex, when it was born, and the home address at the time of death. Space was provided for half a dozen names of mothers who, in the stated locality, gave birth to a child of the same sex in the same month or half-year. These names were to be obtained from official registers of births. When completed, the list might be passed to a health visitor with instruction to visit the houses in the order in which they were listed. If it proved impossible to arrange an interview with the first mother the reason was to be entered on the list and the second house visited. In this way a record was kept of all first and later choices, also the reasons for not obtaining the control of choice.

Survey Objectives

The survey doctors were told that the purpose of the survey was to compare the medical and social histories of the children before and after birth, and that the promoters were interested both in the nature of all "previous" illnesses and in the investigations and treatments associated with them (the schedules had separate headings for diagnoses, antibiotics, and *x*-ray histories).

Interviewing began in December, 1955, and by the following August 547 case/control records had been completed and returned to Oxford. These formed the basis of a preliminary report, which showed that abdominal *x*-ray films in the relevant pregnancy—that is, direct foetal irradiation—had been reported in 85 cases and 45 controls (Stewart, Webb, Giles, and Hewitt, 1956). For records completed after this date the corresponding numbers were 107 and 58. There is therefore nothing to indicate that awareness of an important finding has affected these records.

Preliminary Findings.—The 1,416 case/control pairs completed by May, 1957, included 89 transfers and 28 adoptions. After removing these 117 pairs the remaining 1,299 (on which most of the findings are based) included 619 leukaemias and 680 other cancers. The controls were represented by 775 first choices and 524 later choices. Only 60% of first choices may seem a low proportion, but the birth registers from which the names were taken had been compiled, on average, six or seven years before the survey began. With the use of a register which is revised annually the Survey of Sickness obtained 84% of their first choices (Logan and Brooke, 1957). A quarter of the children wanted as controls had definitely left the district and a further 5% (marked "no reply") may have done so. Only 6% of the mothers either refused to co-operate or were dead, and 3% were deliberately rejected because the child was dead or had always lived away from its mother. However desirable it may be in theory to include such children in the sample, in practice the records would have been so defective that they would have been of very little use for case/control comparisons.

Failure to obtain 100% of first choices has led to deficits in the control group of three types of children—namely, first-born children, migrants, and twins.

First-born Children and Migrants.—The cases included 510 first-born children and the controls 427. By national standards the first figure is nearer expectation (approximately 500) than the second, it is therefore reasonable to suppose that there is a genuine deficit on the control side and that it is related to the fact that one-child families tend to move house more often than larger families. Because of this deficiency we have, wherever indicated, done separate analyses of the first- and later-born children of primiparae and multiparae, and of migrant and static families.

Twins.—The birth registers from which the controls were taken were, in effect, lists of maternities; hence the control group should contain approximately half the normal proportion of twins. The actual number of control twins was 15 and the "expected" number in the region of 28. By this calculation the number of twins in the case group, 33, is higher, but not significantly higher, than the expected number. Though numerically small, the twins are from the point of view of foetal irradiation important. For this reason they are considered separately in Section II.

In spite of the larger number of first-born children in the case group there was no excess of small families. By the time of the survey most of these children had acquired younger brothers and sisters, and the average family size was the same in both groups (see Section VI).

Demographic Characteristics

The following information about the age, sex, and locality distribution of the cases is based not on the survey findings but on death certificate data.

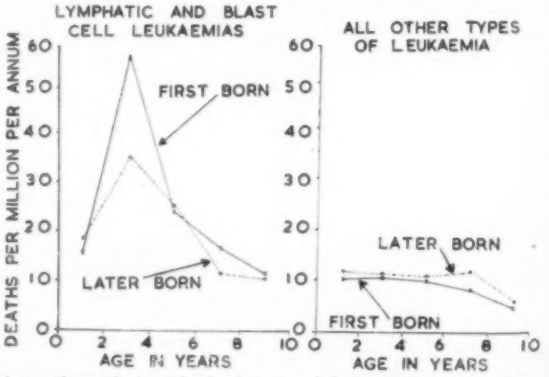
Age and Sex.—The death rates were higher for males than for females and for children under 5 than for children aged 5 to 10. In the leukaemia series the early peak of mortality was shown by a higher death rate for children between 2 and 4 years of age than for younger or older children.

Locality.—Only two regions—Surrey and Manchester—had a suggestive excess of leukaemia deaths, but in general these and the other cancer deaths showed a remarkably even geographical distribution. Classification by size of town revealed greater contrasts, but the highest death rates were in medium-sized towns, not in the largest (see Table I).

TABLE I.—*Comparative Mortality Ratios for Age Group* 0–14 *in Five Density Aggregates,* 1953–5 (*England and Wales* = 100)

	Leukaemia	Other Malignant Disease
Conurbations	108	100
Towns with over 100,000 inhabitants	98	100
" 50,000 to 100,000 inhabitants	124	110
" under 50,000 inhabitants	92	96
Rural areas	86	100
$\chi^2_{(4)}$	12·372	1·451
Value of P	<0·02	>0·80

Birth-rank Distribution.—Since the control group was deficient in first-born children the birth-rank distribution of the cases has been compared with national figures for the years which corresponded to the births of these children—that is, 1943–55 (Registrar-General, 1945–56). According to these statistics, the birth-rank distribution of childhood cancers, other than leukaemia, is typical of the popula-



Approximate leukaemia death rates of first- and later-born children, 1953–5. These rates are based only on 663 leukaemia cases of known parity. The inclusion of 14 adopted cases and 115 cases not followed up would give somewhat higher rates per million but would be most unlikely to change the appearance of the graphs.

tion at large, but among leukaemic children there appears to be a 10% excess of first-born children. Division of these children into two groups—(1) lymphatic and blast-cell leukaemias, and (2) other leukaemias—revealed further peculiarities (see Chart). Thus, between the ages of 2 and 4 years the distribution of lymphatic and blast-cell leukaemias indicates a 70% higher risk for first-born children than for other children. Whether this risk is related to the antenatal or post-natal peculiarities of first-born children we do not know. It is, however, deaths in this narrow age group which are largely responsible for the remarkable post-war increase in childhood deaths from leukaemia both in this country and in the U.S.A. (Hewitt, 1955). Our own data on post-natal *x*-ray exposures (see Section IV) also suggest that some of the children who survive to the age of 2, but are dead of leukaemia before the age of 4, belong to a separate aetiological group.

Maternal Age.—The average age of the mothers at the date of birth of the survey children was 28.91 years for the leukaemia series and 28.43 for the other cancer series—that is to say, the group which contained the higher proportion of primiparae was, on average, 25 weeks *older* than the other group. Further examination of the maternal ages showed that this greater average age was determined by a small group of mothers who were over the age of 40 when the leukaemic child was born. These mothers represented 6.9% of the leukaemic series and only 3.5% of the other cancer series. To avoid confusion with the high incidence of mongolism in the leukaemia series (see Section IV) the mothers of mongols were excluded from the next analysis and primiparae were separated from multiparae. In the latter group (which contained the bulk of the women over 40) the average age was 52 weeks higher for the leukaemia than for the other cancer series, a difference which is statistically significant ($P<0.01$). Assuming that age of the mother has not affected the prevalence of other childhood cancers, this suggests that the risk of dying of leukaemia before the age of 10 years is twice as great as usual if the mother is over 40 years of age at the date of birth (this estimate is in no way dependent on the slightly higher incidence of obstetric *x*-ray examinations in elderly women). The independent findings, first, of a large number of mongols in the leukaemia series, and, secondly, of a relatively large number of "old" mothers in the leukaemia series suggest that childhood leukaemia and mongolism are influenced by a common factor, rather than that one disease predisposes to the other (see also Section IV). In a recent American survey the ages of the mothers in a smaller group of children with leukaemia and others cancers also show these contrasts (Manning and Carroll, 1957).

Social-class Distribution.—The basis of the social-class distribution was the father's occupation. A statement of family income was also obtained for 87% of cases and 88% of controls. Since it is common knowledge that professional families move house more often than working-class families, the social and economic distributions have been calculated separately for children who moved house after they were born (migrant series) and children who did not (static series). On this basis there are virtually no social-class or economic distinctions as between cases and controls or between cases of leukaemia and cases of other cancer. (National mortality rates suggest that leukaemia deaths at later ages tend to have an upward social gradient, and other cancer deaths a slight downward gradient.)

SECTION II. MOTHERS' X-RAY HISTORIES

Although the mothers were questioned first about their children and only later about their own health, we shall deal first with the mothers' *x*-ray histories and illnesses. These were recorded separately for (1) the first period, before marriage; (2) the middle period, between marriage and the relevant conception; and (3) the final period, during the relevant pregnancy. Three categories of exposure were distinguished—therapeutic, occupational, and diagnostic. The first two need not detain us. Only 16 mothers (7 cases, 9 controls) reported any radiotherapy and the treatments never coincided with the relevant pregnancy. A further 19 mothers (12 cases, 7 controls) may have been exposed to *x* rays in the course of their work, and for three—all mothers of cases—the work was continued during the final period. The occupations in question were: nurse in radiotherapy department, nurse in a radiological department, and a metal-tester.

Diagnostic X-ray Histories

A summary of the mothers' diagnostic *x*-ray histories is given in Table II. Figures are given for the three periods, separately and jointly, and for two main types of *x*-ray examination (abdominal and other). The figures are numbers of *mothers*, not numbers of films or examinations—that is to say, no woman has been counted more than once

TABLE II.—*Number of Mothers Reporting X-ray Examination of Different Sites (Abdomen and Other) in Three Periods (see Text)*

Period	*X*-ray Examinations		
	Abdominal	Other	Any
Before marriage	*44/26=*1·69*	335/275=*1·22*	361/296=*1·22*
Between marriage and relevant conception ..	109/121=*0·90*	213/184=*1·16*	304/285=*1·07*
During relevant pregnancy	178/93=*1·91*	117/100=*1·17*	273/184=*1·48*
Any period	296/215=*1·38*	531/456=*1·16*	692/593=*1·17*

The case/control ratio of 1·91 for abdominal *x*-ray exposures during the relevant pregnancy (1) differs from the "expected" ratio (1·00) at the level of $P<10^{-4}$; (2) differs from the contemporary ratio for other *x*-ray exposures (1·17) at the level $P\simeq0{\cdot}011$ and from the ratio for other *x*-ray exposures in any period (1·16) at the level $P<0{\cdot}001$; and (3) differs from the ratio for abdominal *x*-ray exposures in any period (1·38) at the level $P\simeq0{\cdot}012$.
* 44/26, etc., represent ratio of case mothers to control mothers.

in any cell of the Table (consequently the figures for "any period" and "any *x*-ray exposure" are rather lower than the sum of the figures for separate periods and separate types of examination). The figures in italics give the ratios between the numbers of case mothers and the corresponding numbers of control mothers.

It will be seen that 692 mothers of cases reported at least one diagnostic *x*-ray exposure compared with only 593 mothers of controls, a case/control ratio of 1.17. Though this case excess is significant, it is not very large, and might perhaps be attributed to relative under-reporting of *x*-ray exposures on the control side. If, however, under-reporting by control mothers was the only reason for the case excess one would expect to find similar case/control ratios for each type of examination and for each period of life. In fact the ratio is higher for abdominal (1.38) than for other types of examination (1.16), and higher for all examinations during the relevant pregnancy (1.48) than during earlier periods (1.22 and 1.07). In particular, the ratio for abdominal *x*-ray examinations during the relevant pregnancy is outstandingly high (1.91). The chance probability of obtaining so high a ratio is less than one in ten million. Moreover, as the footnote to Table II shows, this ratio is significantly higher than the ratio for *x*-ray examinations of other sites in this period, and than the ratio for abdominal *x*-ray examinations as a whole. Hence there is prima facie evidence that abdominal *x*-ray examinations during pregnancy—the only type of examination involving direct exposure of the foetus—can contribute to the aetiology of malignant disease in children.

Most of the remainder of this section is devoted to further analysis of the apparent association between foetal irradiation and malignant disease in childhood, but it is necessary first to say something about the figures for the other maternal *x*-ray histories.

One group of maternal *x*-ray histories—those relating to *x*-ray exposures of the abdomen during the middle period—shows a small excess on the *control* side. This was at first thought to be due to the fact that on the control side there were more previous children, and hence more occasions for obstetric *x*-ray exposures in the middle period. However, when the obstetric *x*-ray examinations were separated from

the other abdominal *x*-ray examinations belonging to this period and related to the number of pregnancies at risk (see Table III) there was still a slight excess on the control side. This strengthens the view that the control mothers were as efficient as the mothers of cases in recalling their abdominal *x*-ray examinations.

TABLE III.—*Comparison Between Cases and Controls in Respect of Obstetric X-ray Examinations in the Middle Period (i.e., Between Marriage and the Relevant Conception)*

	Cases	Controls
Total No. of previous pregnancies	1,623	1,742
No. of women reporting obstetric (abdominal) *x*-ray examinations between marriage and relevant conception:		
(*a*) Actual	79	96
(*b*) Expected	84·41	90·59

In the pre-marriage period there was a case excess for abdominal *x*-ray exposures which has to be accepted as technically significant ($P<0.05$). The possibility has therefore to be considered that damage to the maternal gonads may increase the risk of childhood malignancy. But even if this is the correct explanation such damage is of minor interest, for, as judged by the numbers involved, its importance can only be one-quarter of that of direct foetal irradiation.

Unlike the case excess for abdominal *x*-ray examinations, that for other *x*-ray examinations showed no tendency to concentrate in the period of the relevant pregnancy. This seems to dispose of the notion that scatter from *x*-ray exposure of sites other than the abdomen had been harmful to the cases. The meaning of the steady case excess in all periods is not clear. To be on the safe side we will assume (see Table VII) that it is an average measure of the relative under-reporting of *x*-ray exposure by control mothers compared with the case mothers. However, even this group is not completely homogeneous as regards case/control comparisons. On further breakdown it was found that mothers reporting chest *x*-ray examinations were in substantial excess on the case side (ratio of 1.20), but that the numbers reporting skull or limb exposures were virtually identical (133 and 132).

The first step in pursuing the association between foetal irradiation and malignant diseases was to check all reports of abdominal *x*-ray examinations during the relevant pregnancy against hospital records. This revealed a few inaccuracies. Five mothers of cases and five of controls were found to have reported an examination which in fact had been performed during a different pregnancy. In a further 14 instances (9 cases and 5 controls) no hospital record of the alleged examination could be found. The figures shown in Table II do not include any of these faulty records (the effect of removing them was to alter the case/control ratio from 1.86 to 1.91).

Twins.—As already explained there are only 15 twins in the control group compared with an expected number of 28 (see Section I). Since seven of these 15 children had been *x*-rayed *in utero* it is reasonable to suppose that with a full quota of twins there might have been six more control mothers reporting abdominal *x*-ray examinations in the final period.

First-born Children.—Separate analysis of the maternal *x*-ray histories in groups defined by parity (Table IV) showed that the proportion of first-born children who were *x*-rayed *in utero* was approximately 2% higher than the proportion for other children. This slight difference is equivalent to about two "extra" records of direct foetal irradiation on the case side.

TABLE IV.—*Histories of Direct Foetal Irradiation, Distinguishing Three Birth-rank Groups of Cases and Controls*

Position in Family of Child (Birth Rank)	Cases		Controls		Ratio
	No.	%	No.	%	
First	85/510	16·7	36/427	8·4	1·99
Second	47/393	12·0	28/448	6·3	1·90
Later	46/396	11·6	29/424	6·8	1·71
All	178/1,299	13·7	93/1,299	7·2	1·91

Migration (see Table V).—Independent case/control comparisons based on the "migrant" and "static" series (see Section I) showed no significant differences between these two groups.

The last point to be considered is whether the high case/control ratio for abdominal *x*-ray examinations in the relevant pregnancy could be due to the existence in the case group of a condition or conditions which only incidentally caused the child to be *x*-rayed *in utero*. In this connexion it is clearly appropriate to draw a distinction between *x*-rays taken for purely obstetric reasons and other abdominal *x*-rays which happened to coincide with the pregnancy (see Table VI). According to this analysis over

TABLE V.—*Frequency of Direct Foetal Irradiation of Cases Belonging to "Migrant" and "Static" Families and of Corresponding Controls*

Foetal irradiation	Migrant Series		Static Series	
	Cases	Controls	Cases	Controls
Yes	57	23	121	70
No	325	359	796	847
Total	382	382	917	917
χ^2	15·205		14·610	
P	<0·001		<0·001	

90% of the *x*-ray examinations were taken for obstetric reasons, other abdominal *x*-ray examinations representing 9% of cases and 6% of controls. Inasmuch as these other abdominal *x*-ray examinations tended to take place earlier and to involve heavier exposures than the obstetric *x* rays, they might be expected to concentrate on the case side if there were a causal relationship between direct foetal irradiation and childhood malignancies. Hence the slight excess of other abdominal *x*-ray exposures on the case side in no way disturbs this hypothesis.*

TABLE VI.—*Numbers of Mothers Reporting Obstetric and Other Abdominal X-ray Examinations During the Relevant Pregnancy*

X-ray Category and Reasons for *X*-ray Examination	Cases		Controls	
	No.	%	No.	%
Obstetric:				
Position	61	36·3	29	34·5
Size (? twins)	53	31·5	29	34·5
Routine pelvimetry	35	20·8	20	23·8
Diagnosis of pregnancy	4	2·4	1	1·2
Total	153	91·0	79	94·0
Other abdominal:				
Barium meal	6	3·6	1	1·2
Intravenous pyelogram	3	1·8	—	—
Injury	4	2·4	1	1·2
Other	2	1·2	3	3·6
Total	15	9·0	5	6·0
Total of all known indications	168	100·0	84	100·0
Indication for *x*-ray examination unknown	10	—	9	—

We are now in a position to judge the effect of all the factors which might possibly have contributed a spurious element to the case/control ratio for abdominal *x*-ray examinations in the relevant pregnancy. To do this we have made three assumptions which are unfavourable to an explanation in terms of a causal link between foetal irradiation and childhood malignancies. These are: (1) that the excess of twins in the case group is wholly spurious; (2) that ill-health during pregnancy is of such overruling impor-

*Judging by the number of deaths among the children of case and control mothers, the older and the younger children of the case mothers were just as healthy as the older and younger children of the control mothers, nor was there any difference in the stillbirth rates for the case and control groups (see Section VII).

tance that any associated *x*-ray exposure should be ignored; and (3) that the case mothers were 16% more efficient than the control mothers in reporting *x*-ray exposures (on the grounds that the case/control ratio for other *x*-ray examinations was 1.16) (see Table II). These three assumptions have been worked into Table VII, which excludes all twins,

TABLE VII.—*Actual (and Expected) Numbers of Cases and Controls With and Without a History of Direct Foetal Irradiation. Revised Basis of Comparison (see Text)*

	Cases	Controls	Total
Irradiated	141 (118·44)	81 (103·56)	222
Not irradiated	1,125 (1,147·56)	1,204 (1,181·44)	2,328
Total ..	1,266	1,284	2,550

$\chi^2_{(1)}$ with continuity correction is 9·644, equivalent to a normal deviate of 3·10; $P < 0·002$.

counts all abdominal *x*-ray examinations in the final period, other than purely obstetric *x*-ray examinations among the non-irradiated totals, and gives "expected" numbers which are calculated not on the basis of equality but on an "expected" case/control ratio of 1.16 to 1.00. In spite of these drastic modifications there is still an excess of abdominal *x*-ray examinations on the case side which is so large that it would occur by chance in less than one of 500 repeated trials.

In the remainder of this section it is assumed that there is a causal relationship between irradiation *in utero* and childhood malignancies, and four aspects of the risk involved are considered: (1) its relationship to *x*-ray dose, (2) its relationship to the maturity of the foetus at the time of exposure, (3) its relationship to the type of malignant disease, and (4) its absolute size.

Dose-Response Relationship

Court-Brown and Doll (1957) have studied the incidence of leukaemia and aplastic anaemia in adults given deep *x*-ray therapy to the spine. Although they had only 37 cases at their disposal they were able to demonstrate a strong relation between dose and risk of disease. The present series of children includes no fewer than 178 in whom malignant disease had been preceded by antenatal irradiation, and therefore appears to offer ample material for studying dosage effects. There is, however, an important difference which nullifies the advantage of larger numbers. Court-Brown and Doll had an almost "pure" series of radiation-leukaemias, since they gave evidence that over 90% of them would not have occurred but for the preceding *x*-ray exposures. In the present series a high proportion of the cases *x*-rayed *in utero* developed the fatal disease for *other* reasons. The existence of these cases is bound to hinder recognition of a dose-response relationship.

Attempts to collect data for the study of dosage effects met with great difficulties. Over 200 different hospitals had to be asked for records, many of which related to events of more than five years previously. Radiologists supplied all the technical details available, but these were rarely sufficient to support a calculation of dose. Finally, we were reduced to using, as an extremely crude index of dose, the number of films believed to have been taken, though even this was often no more than a reasoned guess on the part of the radiologist and did not include films discarded by the radiographer. Table VIII shows a classification of the cases and controls on this basis. Except in the group with no films the numbers are small and therefore the sampling errors of the case-control ratios are large. The group representing three films breaks the rising sequence of ratios, but at least the lowest and highest ratios (0.93 and 3.20) correspond to the lowest and highest number of films (nil and four or more films). A small group of mothers, not distinguished in the table, who had five or more abdominal *x*-ray examinations during the relevant pregnancy, included 15 cases and only 2 controls. Thus the figures are consistent with, though they do not establish, a relationship between increasing dose and increasing risk.

TABLE VIII.—*Distribution of Cases and Controls Irradiated in Utero According to the Numbers of Abdominal Films Reported Taken During the Relevant Pregnancy*

No. of Films	Cases	Controls	Ratio
0	1,121	1,206	0·93
1	37	27	1·37
2	60	26	2·31
3	23	18	1·28
4 or more	32	10	3·20
(Unknown number)	(26)	(12)	(2·17)
Total:	1,299	1,299	1·00

Timing Effects

The precise date of exposure was ascertained in most cases, and on this basis each mother was classified according to the month of the first exposure (see Table IX). The dated series did not include a single mother examined within 28 days of conception, and only 20 mothers were certainly *x*-rayed in the first half of pregnancy. However, in this small group there were 18 cases and only 2 controls, which represents a much higher case/control ratio than the one for exposures in the second half of pregnancy (148 cases, 83 controls). The variations in the second half of pregnancy all lie within the accepted range of chance variation.

TABLE IX.—*Distribution of Cases and Controls Irradiated in Utero According to Month of Pregnancy*

Gestation Period in Months	Cases	Controls	Case/Control Ratio
1st to 5th	18	2	(9.00)
6th, 7th	15	9	1·67
8th	20	19	1·05
9th	55	30	1·83
10th	58	25	2·32
Total known	166	85	1·95
Unknown	12	8	(1·50)
Total ..	178	93	1·91

A statistical comparison of the cases and controls in the five "known" categories above yields $\chi^2_{(4)} = 9·656$, for which $P < 0·05$.

Tissue Sensitivity

Previous work suggests that, in adults, leukaemia is more likely to be produced by ionizing radiations than other malignant diseases (Court-Brown and Doll, 1957; Faber, 1957). But our own data suggest that in a foetus there may be other tissues which are at least as sensitive to *x* rays as the reticulo-endothelial system (see Table X). In this table the cases have been divided into eight diagnostic groups, and the number of irradiated cases in each of these is compared with the number which would be expected if the *x*-ray exposures were evenly distributed among the cases. In calculating these expected numbers, we have standardized them in ten-yearly age groups, in order to allow for changes in *x*-ray habits during the years in which the survey children

TABLE X.—*Comparative Incidence of Direct Foetal Irradiation in Eight Diagnostic Groups*

Diagnosis	No. of Cases	Irradiated *in utero*		
		%	Actual No.	Expected No.
Lymphatic leukaemia	292	14·4	42	40·31
Myeloblastic "	124	7·3	9	16·24
Blast-cell and other leukaemias ..	203	13·8	28	27·93
Lymphosarcoma, other reticuloses ..	109	7·3	8	14·24
Malignant tumours of C.N.S. ..	212	12·7	27	28·75
" " kidney	120	15·8	19	16·68
" " suprarenals (incl. *all* neuroblastomas)	87	18·4	16	12·68
Malignant tumours of other sites ..	152	19·1	29	21·16
Total ..	1,299	13·7	178	177·99

In an 8 × 2 table the comparison of actual and expected numbers irradiated and not irradiated yields $\chi^2_{(7)} = 11·832$, compared with 12·017 at the level $P = 0·10$.

were born. On this basis the differences between the actual and expected numbers are of a magnitude which, under chance conditions, would be expected to occur in about one out of ten samples. The group labelled "other sites" had the highest percentage (19.1%). This included three retinoblastomas with three *x*-ray exposures, and 12 teratomas with seven *x*-ray exposures. We hesitate to draw any conclusion about the retinoblastomas, because in an independent series of 39 children who were said to have survived surgical removal of a retinoblastoma we found there had been only seven pre-natal *x*-ray examinations, which is no more than average for all forms of cancer. However, the chance of obtaining as many as seven *x*-ray exposures in 12 cases is only one in a thousand, so it may be that the nests of embryonic tissue contained in teratomas are exceptionally radiosensitive.

Delayed Effects of Foetal Irradiation

The survey was deliberately restricted to children under 10 years of age because it was thought that this was a convenient limit to the time that mothers might be expected to recollect events. But by so doing we may have missed some of the consequences of direct foetal irradiation. If the effects of pre-natal irradiation are exhausted by the age of 10 years one would expect the case/control ratio for foetal irradiation to be higher for children who were under 5 years of age at the onset date than for children who were 5 or over. But, as Table XI shows, this ratio is 1.73 for the younger children and 2.50 for the older children.

TABLE XI.—*Case/Control Ratio for Direct Foetal Irradiation. Comparison of Cases and Controls Defined by Age at the "Final Date"*

	Cases	Controls	Ratio
Deaths at ages 0 to 4	123	71	1·73
,, ,, 5 to 9	55	22	2·50
,, ,, 0 to 9	178	93	1·91

Estimates of Risk

The following estimates are based on the figures shown in Table II and necessarily represent a rough appraisal of the situation. In the case group 13.7% of the children were *x*-rayed before birth and 86.3% were not. The corresponding percentages for control children were 7.2 and 92.8. On this showing children who have been *x*-rayed *in utero* are $\frac{(13.7 \times 92.8)}{(7.2 \times 86.3)}$ times, or twice as likely to die of a malignant disease before their tenth birthday as other children. Since at the present time about one in every 1,200 children in Britain die in this way, it follows that less than one in a thousand of the pre-natal *x*-ray examinations performed in recent years have led to death from malignant disease before the age of 10 years. An alternative way of expressing this estimate is to say that abdominal *x*-ray examinations of pregnant women have in recent years been responsible for (13.7−7.2) % or between 6 and 7% of all deaths from malignant disease before the age of 10 years.

To sum up: there appears to be no doubt that there is a causal relationship between pre-natal exposure to *x* rays and the subsequent development of malignant disease, and there are indications that the risk is related both to the dose of *x* rays and to the date of exposure. There is nothing to suggest that irradiation *in utero* explains the early peak of leukaemia mortality (see Section IV for data on post-natal *x*-ray exposures) and it may even cause deaths from malignant disease after the age of 10 years. The rough estimates of risk which are given here apply only to one period of time and to the *x*-ray doses in use at that time. Evidently radiotherapy of pregnant women is an extremely rare event in this country, and contributed nothing to the cases we have considered.

[ADDENDUM.—After this report had been written we received the results of an independent study (Paterson, 1958) which had been designed specifically to test the conclusion announced in our preliminary communication. This study concerned children who had died under the age of 10 in the State of Louisiana during the years 1951–5. Although conducted on a rather small scale it had one important advantage over our own inquiry: all the information was obtained direct from professional sources, thus minimizing the risk from emotional bias or selective memory in the informants. The incidence of irradiation *in utero* discovered by Paterson was as follows: among 77 children who died of leukaemia, 27.3%; among 70 children who died of other cancers, 28.6%; and among 293 control children who died of other causes, 18.4%. These percentages are much higher than those found in England and Wales, but show two important resemblances: (1) the significantly higher incidence of foetal irradiation among children with malignant disease than among controls, and (2) similar figures obtained for children with leukaemia and those with other forms of malignant disease. Using Paterson's figures in the same way as our own to derive an estimate of the relative risk of malignant disease associated with irradiation *in utero*, we have $\frac{27.9}{18.4} \times \frac{81.6}{72.1} = 1.72$, which is in reasonable agreement with our own estimate.]

SECTION III. MOTHERS' ILLNESSES

The mothers were asked whether they had ever had a serious illness or injury before the survey child was born. Although these events were actually recorded separately in the three periods (see Section II), only two periods are distinguished in the following analysis—namely, before and during the relevant pregnancy. Only information of a reasonably objective and definite type has been considered, and unless a common childhood infection—for example, measles—coincided with the relevant pregnancy it has been omitted from the following analyses. After omission of these items and such vague conditions as nervous breakdowns, influenza, anaemia, and injuries other than fractures, approximately half the mothers were left with no diseases before the birth of the survey child. The remaining records were classified according to the *International Classification of Diseases* (World Health Organization, 1949), and the results are shown in Table XII.

TABLE XII.—*Illnesses of Mothers Arising Before and During the Relevant Pregnancy*

International Classification Main Category	Arising Before Relevant Pregnancy		Arising During Relevant Pregnancy	
	Cases	Controls	Cases	Controls
I. Infective	86	82	13	1
II. Neoplasms	9	11	2	2
III. Allergic, etc. ..	24	22	1	3
VI. Nervous system ..	32	37	1	0
VII. Circulatory	53	44	0	4
VIII. Respiratory	219	207	12	13
IX. Digestive	74	91	12	4
X. Genito-urinary ..	62	44	0	0
XI. Pregnancy	32	32	113	77
XII. Skin	33	43	5	5
XIII. Bones and muscles ..	15	20	3	0
XIV. Congenital	5	7	—	—
XVII. Accidents	48	57	0	0
Total No. of illnesses	692	697	162	109
,, ,, women	565	554	155	104

Illnesses Originating Before the Relevant Pregnancy.—The total number of illnesses in this category was 1,389 (cases 692 and controls 697) and the number of mothers affected was 1,119 (cases 565 and controls 554). Unlike the series reported by Manning and Carroll (1957) there were no case/control differences for allergic conditions (category III), but compared with this American series the incidence of these conditions was low. The only group of illnesses with a substantial difference between cases and controls was category X (diseases of the genito-urinary system) with 62

records for cases and 44 for controls. The difference was confined to disease of the renal tract as such (49 cases and 30 controls), which represents a significant case excess (P approx. 0.04).

Illnesses Arising During the Relevant Pregnancy.—The total number of illnesses recorded in this period was 271 (162 cases, 109 controls) with 259 mothers affected (155 cases, 104 controls). Further analysis of the records showed that this case excess, which is statistically significant, was restricted to two categories—namely, infective disease (13 cases, 1 control) and direct complications of pregnancy (113 cases, 77 controls). The latter group (see Table XIII) is

TABLE XIII.—*Illnesses of Mothers Specifically Associated With the Relevant Pregnancy*

I.C.D. Numbers	Illness	Leukaemia		Other Cancers		Total	
		Cases	Controls	Cases	Controls	Cases	Controls
642	Toxaemias of pregnancy ..	29	31	38	26	67	57
640–641	Infections of genito-urinary tract during pregnancy ..	8	3	11	7	19	10
648·0	Threatened abortion ..	14	4	13	6	27	10
Total	.. ..	51	38	62	39	113	77

dominated by toxaemias of pregnancy (67 cases, 57 controls), but there were also 29 urinary infections (19 cases, 10 controls) and 37 threatened abortions (27 cases, 10 controls). The difference between cases and controls is not significant for toxaemia of pregnancy, and the difference for urinary infections is complicated by the fact that six of the mothers on the case side had also had an abdominal *x*-ray examination during the relevant pregnancy (mostly intravenous pyelograms). This leaves threatened abortions and infective diseases as the only ones with a significant and unambiguous excess on the case side. The infective disease group included 10 virus infections on the case side and one on the control side. These undated infections were associated with the childhood diseases shown in Table XIV.

TABLE XIV.—*Infections During the Relevant Pregnancy*

Maternal Infection	No. of Cases	Corresponding Children
Rubella	3	Congenital sarcoma of mediastinum Neuroblastoma at 12 months Lymphoblastoma at 15 months
Mumps	2	Congenital sarcoma of the meninges Leukaemia at 5 years
Herpes zoster ..	4	Healthy control Leukaemia at 7 years Leukaemia at 8 years Cerebral tumour at 6 years
Infective hepatitis ..	2	Leukaemia at 4 years Cerebral tumour at 6 years

To summarize: there is nothing in the illness records to suggest that the case mothers were, before the relevant pregnancy, less healthy than the control mothers. During the relevant pregnancy they appear to have suffered more from threatened abortions and virus infections than the control mothers, but the numbers involved are small.

SECTION IV. CHILDREN'S X-RAY HISTORIES

As already stated, the survey doctors had been told to record the illnesses of the children up to but not beyond the onset dates, these being defined as the dates on which the corresponding children first showed signs of the fatal disease. (In the following analyses the years before this date are referred to as the *pre-onset* period.) Since it was more likely that the mothers of the living children would mistakenly include events after this date than the mothers of dead children, we have in the following analyses discriminated carefully between accurately dated *x*-ray exposures and illnesses and those in which there was a margin of error. We will deal first with non-medical *x*-ray and then with medical *x*-ray exposures, but pedoscope exposures will be mentioned in both parts.

Non-Medical X-ray Exposure.—Three non-medical sources of ionizing radiations were considered—television sets, luminous clocks or toys, and pedoscopes. Only one fact relating to these (undated) exposures has been analysed—namely, whether the child was ever exposed during the pre-onset period. For each of the three sources there was a slight excess on the control side. In the case of television sets (278 cases and 301 controls) and luminous objects (328 cases and 333 controls) the differences were negligible, and even for pedoscopes (212 cases and 242 controls) they were not significant (P approximately 1 in 7). As, however, the exposures were undated, it is possible that the few extra cases in the control side represent exposures which occurred after the onset date. The possible effects of this type of mistake on the pedoscope records are considered again at the end of this section.

Medical X-ray Exposure.—Records of diagnostic and therapeutic *x*-ray exposures were comparatively uncommon, but a slight excess was shown on the case side (see Table XV). The excess was confined to 11 children having radiotherapy (8 cases, 3 controls) and 167 children who had been radiographed on more than one occasion (90/77). For single radiographic examinations there was a slight deficiency of cases (88/100).

TABLE XV.—*Numbers of Children With Post-natal Medical X-ray Exposure*

Type of Exposure	Leukaemia		Other Cancers		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
Diagnostic:						
Once*	43	42	45	58	88	100
More than once	47	38	43	39	90	77
Therapeutic ..	5	1	3	2	8	3
Total ..	95	81	91	99	186	180

* Includes some children for whom the number of examinations was not ascertained.

Tissue Sensitivity.—When a child is *x*-rayed *in utero* it is safe to assume that the whole body has been exposed; but after birth this rarely happens. It was therefore appropriate to examine the records for an association between the parts of the body *x*-rayed after birth and subsequent developments. We have, however, searched the records in vain for any sign of this.

Estimate of Dose.—No attempt was made to discover the number of films taken at each *x*-ray examination or to check the doses used in radiotherapy. The latter were all of the type to treat minor skin conditions, and no examples of deep *x*-ray treatments of the kind recently followed up by Simpson and Hempelmann (1957) were recorded. The 11 children with histories of radiotherapy were all girls treated for naevi. The cases included five leukaemias, one glioma, one neuroblastoma, and one sarcoma of the umbilicus (not the site exposed to *x* rays). At least eight of these children (possibly nine) were treated before their first birthday, and two (both cases) had already been *x*-rayed *in utero*.

Time Relationship

In view of the evidence already presented that a foetus may be specially radiosensitive, the post-natal *x*-ray exposures (diagnostic and therapeutic combined) were analysed by age at first exposure (see Table XVI) to discover whether there were any time relationships. Included in this table are 67 children (27 cases, 40 controls) who have been classified as "age at first exposure unknown." These children were definitely *x*-rayed before the onset date, but the possible dates covered a period of more than 12 months. The remaining children included 128 where the month and year of the first *x*-ray exposure was known, and 171 where the date was given to within 12 months. In the latter group we have assumed that the actual date of exposure was midway between the two possible extremes and have placed the

TABLE XVI.—*Distribution of Children With Post-natal Medical X-ray Exposure According to Age at First X-ray Exposure*

Age at 1st Exposure	Leukaemia		Other Malignant		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
0–	19	12	23	13	42	25
1–	21 } 57	10 } 31	12 } 50	15 } 43	33 } 107	25 } 74
2–	17	9	15	15	32	24
3–	6	4	10	13	16	17
4–	5	14	9	8	14	22
5–	5	9	5	6	10	15
6–	5 } 25	3 } 33	2 } 27	3 } 33	7 } 52	6 } 66
7–	3	2	1	3	4	5
8–	1	1	0	0	1	1
9–	0	0	0	0	0	0
Not known	13	17	14	23	27	40
Total ..	95	81	91	99	186	180

child accordingly. The last two columns of the table (where all cases and all controls are compared) show a significant excess on the case side of children exposed before their third birthdays. This excess is greater for the leukaemic children than for the children with other cancers. For first exposures between fourth and tenth birthdays the balance is on the control side, but the absolute and relative difference is small and may well be due to chance. In the interpretation of these figures much depends on the 67 children whose first exposures were inadequately dated. If the first exposure dates for these children were distributed in roughly the same way as in the dated series it would strengthen the impression of a genuine difference between early and later exposures, but if the distribution were markedly different it might have the opposite effect.

No such reservations need apply to the figures in Table XVII. Here the children have been placed according to their age in years at the onset date, and only three children have had to be relegated to the "age unknown" category. In three of the five age groups there were more cases than controls, and in two there were more controls than cases, but the most striking case/control difference relates to children who were aged between 2 and 3 years at the onset date (58 cases, 27 controls).

A similar arrangement by age at the final date (which was usually within a few weeks or months of the onset date) also picked out children who died between the second and fourth birthdays (51 cases, 24 controls), and again the difference was more marked for leukaemia than for other cancers. This is particularly interesting, since it is precisely this age group which has borne the brunt of the recent increase in childhood leukaemia mortality both in this country and in the U.S.A. (Hewitt, 1955).

TABLE XVII.—*Distribution of Children With Post-natal Medical X-ray Exposure According to Age of the Child at the Onset Date*

Age at Onset Date (Years)	Leukaemia		Other Malignant		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
0, 1 ..	6	7	14	10	20	17
2, 3 ..	35	11	23	16	58	27
4, 5 ..	23	25	21	32	44	57
6, 7 ..	17	22	17	27	34	49
8, 9 ..	14	15	15	13	29	28
Not known	0	1	1	1	1	2
Total ..	95	81	91	99	186	180

* The onset date is defined as either the date of onset of the fatal illness (case children) or the date when the corresponding case developed its fatal illness (control children).

Thus far the evidence in favour of a link between childhood malignancies and post-natal *x*-ray exposure has depended on case/control comparisons of arguable validity. We have therefore attempted to assess the evidence by means of comparisons within the case and the control series, using the following argument. In a "normal" group of children, such as our own controls, the percentage who have ever been *x*-rayed should steadily increase with age, for each year adds to the number of children who are *x*-rayed for the first time. For the sake of simplicity we shall assume that the percentage of "first" *x*-ray exposures is normally the same in each of the first ten years of life. In order to test this assumption we have calculated for the control children the "expected" percentages of children ever *x*-rayed in each of the five age groups shown in Table XVII. In the first two columns of Table XVIII these expected figures are shown in italics together with the actual

TABLE XVIII.—*Distribution (by Age at Onset Date) of Children With Post-natal X-ray Exposure Compared With the Distribution Expected on the Basis of a Regular Increase with Age of the Percentage of Children Ever X-rayed Since Birth*

Age of Children at Onset Date (Years)	Controls		All Cases		Leukaemia		Other Cancers	
	Actual / *Expected*		Actual / *Expected*		Actual / *Expected*		Actual / *Expected*	
	%	No.	%	No.	%	No.	%	No.
0, 1	4·9 *3·5*	17 *12·28*	5·8 *3·7*	20 *12·76*	4·4 *3·8*	6 *5·25*	6·7 *3·6*	14 *7·43*
2, 3	7·2 *10·6*	27 *40·03*	15·4 *11·0*	58 *41·61*	17·9 *11·4*	35 *22·37*	12·7 *10·7*	23 *19·30*
4, 5	19·7 *17·7*	57 *51·15*	15·2 *18·4*	44 *53·16*	16·1 *19·0*	23 *27·20*	14·4 *17·8*	21 *25·95*
6, 7	25·9 *24·8*	49 *46·83*	18·0 *25·8*	34 *48·67*	18·3 *26·6*	17 *24·77*	17·7 *24·9*	17 *23·89*
8, 9	32·2 *31·9*	28 *27·71*	33·3 *33·1*	29 *28·80*	31·1 *34·2*	14 *15·41*	35·7 *32·0*	15 *13·44*
Total	13·8 *13·8*	178 *178·00*	*14·4* *14·4*	185 *185·00*	15·4 *15·4*	95 *95·00*	13·4 *13·4*	90 *90·01*
$\chi^2_{(4)}$ Value of P	7·622 >0·10		19·414 <0·001		12·478 <0·02		11·015 <0·05	

percentages and numbers. It will be seen that the correspondence between the two sets of figures is not exact but lies well within the limits of chance fluctuation (P>0.1). It follows that the original assumption is a reasonable one. Now, if the post-natal *x*-ray exposure had *not* influenced the risk of the children dying later of malignant diseases, the correspondence between the actual and expected figures for the case series should be much the same as in the control series. But the discrepancies are much greater in the case series than in the control. Subdivision of the cases into leukaemias and other cancers shows that in the second age group of the leukaemia series (which includes children who developed leukaemia between their second and fourth birthdays) the proportion of "*x*-rayed children" is actually higher than the proportion in the third age group, although for these children the period during which they had an opportunity to be *x*-rayed was half as long again. For children with other cancers the largest discrepancy is in the first age group, where the actual number of children *x*-rayed (14) is nearly twice the expected number (7.43).

In earlier parts of this paper (and again in Section IV) we discuss evidence which indicates that the decisive factor in some of the cases, particularly in the leukaemia series, dates back to a period well before birth. If this is so then there must be, in the newborn population, a number of children in what may be loosely called a "pre-malignant state." The present analysis of post-natal *x*-ray exposures suggests that if such children are *x*-rayed during infancy overt signs of the disease may appear relatively quickly.

This inference can be drawn from the tables already given, but is perhaps better illustrated by the distribution of cases and controls according to the interval between the first post-natal *x*-ray exposure and the final date. For children *x*-rayed in the first three years of life this was :

Interval, First Exposure to the Final Date	Cases	Controls
Up to 11 months	12	11
12 to 47	62	26
Longer intervals	33	37

This interpretation would also explain the deficiency on the case side of *x*-rayed children who developed the fatal disease between their fourth and eighth birthdays (see Table XVII). For, if irradiation in infancy hastens overt signs of the disease, then there must be some "vulnerable" children who survive a comparatively long time partly because they have not been *x*-rayed. If this is so, we would expect the percentage of *x*-rayed children in the older half of the case series to be below the level for healthy children.

Pedoscopes

We must now reconsider the records for shoe-shop *x*-ray exposures. The same rays are emitted from pedoscope machines as from diagnostic *x*-ray sets. If, therefore, the medical *x*-ray examinations have had an effect, one would expect the pedoscope records to show the same signs. A possible reason for there being no such excess has already been mentioned—namely, inclusion on the control side of children whose first pedoscopic examination was later than the onset date. Another reason should now be apparent. The data on medical *x*-ray examinations suggest a risk only when the first exposure takes place before the third birthday—that is to say, during a period when very few children will have had shoe-shop *x*-ray exposures. The relevant data cannot be analysed by age at first exposure, but if the cases with pedoscope exposures are examined in relation to the age at death some suggestive figures emerge. Only seven children dying before the age of 2 had been *x*-rayed in a shoe-shop, but six of them had leukaemia. The other pedoscope histories included 37 children who developed leukaemia between 2 and 4 years of age (18% of such cases), but only 17 (or 10%) of the children who developed other cancers between these ages. Thus there is no inconsistency between the figures for medical and shoe-shop *x*-ray exposures.

Comment

To sum up: there are two reasons for thinking that *x*-ray films taken shortly after birth influence the distribution of childhood deaths from malignant disease. In the first place, there is a significant case excess for *x*-ray exposures during infancy. Secondly, children who died of leukaemia at the age of 2 and 3 years were concentrated within the group of cases exposed to *x* rays in infancy. The effect of post-natal *x*-ray exposure appears to be more marked in respect of leukaemia than other cancers and to be much weaker than the effect of pre-natal *x*-ray exposure. It may in fact be restricted to speeding the date of death in children who are already predisposed to leukaemia.

The lack of any association between the parts of the body exposed to *x* rays and subsequent developments may be related to the fact that in infancy the reticulo-endothelial system is so widespread that it is likely to be involved in any exposure.

SECTION V. CHILDREN'S ILLNESSES AND THEIR TREATMENT

In this section we consider: (1) congenital defects, (2) acquired diseases during the pre-onset period, and (3) two classes of drugs—sulphonamides and antibiotics. Again we discriminate between accurately dated illnesses and ones which might have happened after the onset date.

Congenital Defects

These were mentioned in 75 of the case and 46 of the control records, but only two conditions, mongolism and naevi, were more common among the cases.

Mongols.—There were 17 mongols in the leukaemia series, one among the other malignant disease, and none in the control group, though one child placed first on a control selection list was said to be a mongol and to have been in an institution since infancy, and was for this reason not chosen (see Section I). Until two years ago only four cases of leukaemia associated with mongolism had been reported. Since then Krivit and Good (1956), Merrit and Harris (1956), Carter (1956), and Paterson (1958), have between them reported 13 cases. With the present series this makes a total of 34 reported cases. Since the incidence of mongolism in the present leukaemia series (2.6%) is nearly 20 times as high as the incidence of mongolism in 14,000 consecutive births (Malpas, 1937), the association is evidently not a fortuitous one. We have already shown that excessive maternal age at the time of the child's birth (which undoubtedly predisposes to mongolism) also predisposes to leukaemia (see Section I). It is therefore more likely that the two diseases are influenced by a common factor than that the antecedent condition, mongolism, predisposes to the later condition, leukaemia. If this is so then for some of the cases of leukaemia the decisive event must date back at least to the onset of the mongolism; that is to say, at the latest to the second month of gestation. A number of facts relating to the mongols in the survey are shown in Table XIX. The mongol who developed a

TABLE XIX.—*Features of the 18 Mongols Included in the Survey*

Cause of Death	Cell Type (Leukaemias)	Sex	Birth Rank	Age at Death	Age of Mother*
Cerebral glioma	—	M	4	3 years 5 months	40
Leukaemia	Myeloid	M	7	2 ,, 11 ,,	44
,,	,,	M	2	1 year 2 ,,	44
,,	Lymphatic	F	8	1 ,, 6 ,,	43
,,	,,	F	4	5 years 0 ,,	42
,,	Myeloid	M	5	2 ,, 1 ,,	40
,,	N/R	F	2	2 ,, 8 ,,	39
,,	Lymphatic	M	3	1 year 11 ,,	38
,,	,,	M	2	4 years 9 ,,	36
,,	Monocytic	M	2	5 ,, 11 ,,	34
,,	Lymphatic	F	1	2 ,, 0 ,,	34
,,	Myeloid	F	4	2 ,, 6 ,,	34
,,	Lymphatic	F	1	2 ,, 0 ,,	32
,,	,,	F	2	1 year 5 ,,	32
,,	Aleukaemic	F	3	8 years 4 ,,	29
,,	Lymphatic	M	1	6 ,, 5 ,,	26
,,	Monocytic	M	1	4 ,, 6 ,,	26
,,	Lymphatic	M	1	6 ,, 11 ,,	19

* Age at birth of survey child.

glioma had been *x*-rayed 71 days before birth, but none of the mongols who died of leukaemia had been irradiated *in utero*. Four mothers had had previous abortions, but there were no threatened abortions in the relevant pregnancy and no previous stillbirths. One mother was married to a second cousin.

Naevi.—These were reported 34 times on the case side and 21 times on the control side. As previously stated, eight of the cases and three of the controls were treated with *x* rays. The overall difference between cases and controls is not statistically significant, and might be due to under-reporting on the control side of a condition which is only cosmetically important. For girls there were 18 cases and 14 controls, and for boys 16 cases and 7 controls.

The other congenital defects took various forms and were evenly distributed between the two series, with 25 records on the case side and 25 on the control side.

Other Diseases of Childhood

It was clearly important to exclude all illnesses which happened after the onset date. This raised two problems: what to do with an illness which appeared to coincide with the onset of the fatal disease; and what to do with an inaccurately dated event which might or might not have preceded this date. An illustration of the first problem is provided by a case record which stated: "Following measles the child was always ailing. The measles was complicated by pneumonia then . . ." In this case we should have placed the onset date immediately after the measles and excluded all subsequent events, even the so-called pneumonia.

The second problem arose when an illness was not more precisely dated than the year in which it happened or the age, in years, of the child at the time. In such cases we have assumed that the event occurred midway between the limiting dates. It follows that an illness dated, say,

"1953" would have been counted in the pre-onset period if the onset date was July 1 or later, but not otherwise. Similarly an illness occurring "at 4 years of age" would be counted in the pre-onset period if the onset date was 4 years and 6 months or over, but not otherwise.

It follows that, though some illness must have been wrongly placed, the errors in placing are likely to have cancelled out, leaving an approximately correct total in the two series; where there was possible confusion between a previous illness and an early but unrecognized manifestation of the fatal disease, the illness has not been included in the following analyses.

In Table XX the illnesses allocated to the pre-onset period have been classified as *recent* if within two years of the onset date, and *remote* if two or more years before this date. Events which could not be placed in one or other of these subgroups have been relegated to a separate column and are not included in the total of dated illnesses. The table deals with illnesses, not injuries, and is restricted to relatively acute episodes which could be more or less precisely dated. A number of chronic diseases, injuries, operations, and ill-defined conditions not included in the table are mentioned in the text.

The first part of Table XX deals with the six infectious diseases which comprise nearly 80% of all dated illnesses and of all illnesses in the *recent* period. The exclusion of

TABLE XX.—*Childhood Illnesses in* 1,299 *Pairs of Survey* (*M*) *and Control* (*C*) *Children*

	Illness Within 2 Years of Onset Date		Illness More than 2 Years Before Onset Date		Total of Dated Illnesses		Additional Illnesses of Uncertain Date	
	M	C	M	C	M	C	M	C
Measles	208	235	236	219	444	454	60	70
Chicken-pox	131	173	125	102	256	275	46	55
Whooping-cough	105	136	154	158	259	294	48	36
Mumps	57	61	45	38	102	99	10	22
Rubella	47	46	34	34	81	80	12	23
Scarlet fever	20	24	19	15	39	39	4	6
Total	568	675	613	566	1,181	1,241	180	212
Bronchitis	38	24	19	19	57	43	6	3
Bronchopneumonia	39	17	37	32	76	49	2	1
Total	77	41	56	51	133	92	8	4
Acute tonsillitis	30	22	14	12	44	34	1	4
Acute otitis media	20	25	15	9	35	34	0	2
Total	50	47	29	21	79	68	1	6
Other infections	88	54	65	47	153	101	12	9
Other illnesses	29	12	29	12	58	24	1	3
Total	117	66	94	59	211	125	13	12
Grand total	812	829	792	697	1,604	1,526	202	234

M = Survey children (all malignant diseases). C = Controls.

cases of uncertain date has still left an excess on the control side, but this is slight and confined to three diseases —measles, chicken-pox, and whooping-cough. As this comparison might have been affected by the deficit of first-born children in the control group, a rough standardization for birth rank was made. This had very little effect, particularly on the comparison between illnesses which happened within two years of the onset date, where the difference between cases and controls was mainly concentrated. Hence the popular idea that an infectious illness occasionally initiates a malignant process (or provokes a pre-malignant state) receives no support from the present survey. To argue the other way and say that the survey findings suggest an antagonism between exanthema and malignant diseases would also be wrong. Only in the *recent* period and for one disease (chicken-pox) was there a significant excess of controls, and for this disease there was a deficiency of control records in the *remote* period, which reduces the overall excess to a non-significant level.

The second part of Table XX shows that acute pulmonary infections were relatively uncommon, but for every three cases with such infections there were only two controls. In the *recent* period there were nearly twice as many records of acute bronchitis or pneumonia on the case side, and in the leukaemia series (not distinguished in the table) the case/control contrast was greater than in the other malignant series. Compared with all controls, the excess in the leukaemia series was highly significant ($P<0.001$) and indicates in this series an "extra" 24 cases of acute bronchitis or pneumonia in the two years before the onset date. If this is accepted as evidence of a causal relationship, then about 4% of leukaemia cases might be ascribed to a recent acute pulmonary infection. The corresponding figure (less than 2%) for other cancers was of borderline significance. Since there is no excess on the case side of acute pulmonary infections in the *remote* period, the recent infections are more likely to have accelerated overt signs of malignant diseases in vulnerable children than to have initiated the malignant process.

These estimates all relate to single acute episodes. A much smaller number of children were said to have recurrent attacks of bronchitis (often associated with teething), and these were also in the ratio of approximately three cases to two controls. Such reports are necessarily suspect and difficult to date, so the excess is less certainly a genuine finding. Nevertheless for three infections of the respiratory tract, which were suspect in the same way, there was an excess on the control side: these were "frequent colds" (242/295), "recurrent sore throat" (27/39), and "sinusitis" (10/21).

Clear-cut acute attacks of tonsillitis and otitis media are shown in the third part of Table XX. The slight excess of tonsillitis on the case side is confined to the *recent* period, and the figures for otitis media are roughly equal on the two sides. Not mentioned in the table are 35 case children and 29 controls who had their tonsils removed within two years of the onset date, also 10 cases and 19 controls with chronically discharging ears.

The fourth part of Table XX includes a number of illnesses which were either too rare or too vaguely described to be considered separately. In both periods there was a marked excess on the case side, but since the risk of "inflated reporting" by bereaved mothers is probably at a maximum with minor or ill-defined conditions (which form the bulk of this section), we prefer to draw no conclusions from these figures. Trivial conditions not included in the table are "feeding difficulties" (254 cases, 198 controls), allergic conditions (28 cases, 25 controls), worm infections (89 cases, 82 controls), and frequent colds (already mentioned). The even distribution of cases and controls for three of these four conditions does not suggest under-reporting on the control side; it is therefore possible that the figures in the fourth section of Table XX and the figures for recurrent attacks of bronchitis indicate a genuine excess on the case side.

Finally, some reference must be made to injuries and operations. A vast number of minor injuries, including bruises, were recorded, but only two types were regarded as important enough to merit analysis, and then only if they happened within two years of the onset date. In this period there were 44 fractures (26 cases, 18 controls) and 28 burns or scalds (16 cases, 12 controls). The case excess lay entirely within the leukaemia series, and for the two items combined these children produced 28 records, compared with 14 for the children with other cancers. For recent operations, other than tonsillectomy, the figures were 16 cases and 17 controls.

In summary: Neither in their lifetime as a whole, nor in the two years immediately preceding the fatal illness, did the children with leukaemia and other cancers have an excessive number of the common infectious diseases of childhood. If anything they experienced less chicken-pox and fewer throat and ear infections than usual. On the other hand, the children with leukaemia had a noticeable heavy incidence of acute pulmonary diseases and severe injuries during the two years before they showed signs of the fatal disease.

Sulphonamides and Antibiotics

There were three reasons why the interviewing doctors were specifically asked to record treatments with sulphonamides and antibiotics. In the first place, being new drugs, they might have contributed to the recent increase in leukaemia mortality. Secondly, intensive treatment with sulphonamides occasionally causes aplastic anaemia. Finally, it was thought that the mother would know, if not what exactly was given to the child, at least whether sulpha drugs or penicillin had been prescribed, and how these drugs had been administered.

In the following analyses we have omitted all local applications (drops, powders, and ointments) and made no distinction between oral and parenteral administrations. The conventions which were used to decide whether the drugs were actually given in the pre-onset period were the same as for the illnesses but, as Table XXI shows, there was a

TABLE XXI.—*Treatment of Children's Illnesses with Sulphonamides and Antibiotics*

Treatments	Leukaemia (619 Pairs)		Other Cancers (680 Pairs)		Total (1,299 Pairs)		Case/Control Ratios
	Cases	Controls	Cases	Controls	Cases	Controls	
Sulphonamides:							
Adequately dated ..	94	96	84	61	178	157	1·13
Not adequately dated	30	18	26	34	56	52	1·08
Total ..	124	114	110	95	234	209	1·12
Antibiotics:							
Adequately dated ..	109	83	95	77	204	160	1·28
Not adequately dated	36	36	29	41	65	77	0·84
Total ..	145	119	124	118	269	237	1·14

higher proportion of undated drugs than illnesses. This is due to the fact that in some of the records it was impossible to say which of the dated illnesses had been treated in this way. The table reveals an even distribution of adequately dated treatments with sulphonamides, but the corresponding figures for antibiotics show a small case excess. Since the high incidence of pulmonary infections on the case side was likely to have influenced these figures, Table XXII has been

TABLE XXII.—*Sulphonamide and Antibiotic Treatments, Distinguishing Children Who Had an Acute Pulmonary Infection Within Two Years of the Onset Date*

	All Cases		All Controls		Ratio*
	No.	%	No.	%	
Sulphonamide:					
Children who had acute pulmonary infection within 2 years of onset date ..	22/77	28·57	10/41	24·39	1·17
Remainder	156/1,222	12·77	147/1,258	11·69	1·09
Antibiotics:					
Children who had acute pulmonary infection within 2 years of onset date ..	36/77	46·75	13/41	31·71	1·48
Remainder	168/1,222	13·75	147/1,258	11·69	1·18

* Case/Control incidence ratio.

prepared in which the children who had such an illness in the two years before the onset date are shown separately. The effect of doing this is to reduce the case/control ratio for antibiotics from 1.28 (all treatments) to 1.18 (treatments other than those probably but not certainly related to a recent pulmonary infection). At this level it is within the conventional limits of chance fluctuation (P = approximately 1 in 15). The relatively high case/control ratio for both types of drugs in this table probably reflects the fact (not yet mentioned) that in the case series these infections were usually more severe, as well as more numerous, than in the control series, and for this reason were more likely to receive antibiotics or sulphonamides.

A record was also kept of treatments with ultraviolet light. These were reported for 50 cases and 40 controls. No conclusions can be drawn from these small numbers.

We conclude that there is no evidence for a direct relationship between childhood malignancies and the drugs considered here. There may, however, be an indirect relationship between antibiotics and leukaemia. In recent years antibiotics have revolutionized the prognosis for acute pulmonary infections and have undoubtedly kept alive children who would otherwise have died. If these infections occasionally provoke a latent leukaemic process, then, by increasing the number of children who survive, antibiotics may indirectly increase the prevalence of leukaemia.

SECTION VI. FEEDING HABITS AND HOME BACKGROUND OF THE SURVEY CHILD

Concern is often expressed about the widespread use of new chemicals, particularly food preservatives and detergents, on the ground that these may be carcinogenic. In the present survey no attempt was made to collect information about exposure to specific chemicals, but the mothers were asked a number of questions about their own habits and what they allowed their children to eat and drink.

Feeding Habits

The survey doctors were told to ask whether the children had been given certain foods and drinks every day, less than daily but at least one a week, less often, or never. They were also asked to state when these foodstuffs were first given; and what the mother thought the child had consumed in the way of coloured sweets. The completed records showed that a few control mothers had reported foods which were so unlikely to have been given during the pre-onset period—for example, fish and chips before the age of 1—that the analysis has been restricted to case/control pairs for whom the age at the onset date was not less than an arbitrarily chosen "qualifying age" for each foodstuff (see Table XXIII).

TABLE XXIII.—*Feeding Habits. Percentage of Cases and Controls Who Had Ever Taken Certain Foodstuffs*

Item	Qualifying Age	% of Children Who Had Ever Taken This Item		$\chi^2_{(1)}$	P Approx.
		Cases	Controls		
Dried milk	3 days	69·6	67·1	1·718	0·19
Fruit juice	1 month	90·6	90·7	0·002	0·96
Tinned sieved vegetables ..	4 months	61·1	58·2	1·976	0·16
Other tinned vegetables ..	12 ,,	55·1	60·6	6·797	0·009
Highly coloured cakes ..		33·5	33·7	< 0·001	> 0·98
Highly coloured fruit drinks		47·4	52·6	5·729	0·017
Coloured sweets * ..		32·6	33·0	0·018	0·90
Shop-fried fish and chips		43·2	43·9	0·066	0·79
Total ..				16·306	0·05 > P > 0·02

* For this item "ever" = more than ¼ lb. (113 g.) per week.

The figures shown in this table relate to children who had ever been given a food regardless of the reported frequency. In aggregate the case/control differences for the eight foodstuffs considered appear to be statistically significant ($P<0.05$), but only two foods—tinned vegetables and coloured drinks—showed a significant difference, and both were reported more often on the control than on the case side. For these two items the qualifying age may have been set too low, thus permitting some upward bias on the control side. If such bias exists the case/control ratios for other items may have been underestimated, but the reported percentages are so nearly level that it is unlikely that any important differences have been missed.

The foodstuffs listed on Table XXIII were also considered from the point of view of "dosage." Three of them showed a case excess in the highest consumption category:

Coloured Cakes.—Daily consumption of these was reported for 45 cases and 16 controls, but when this and the next-highest "dose" were combined the figures became 125 cases (11.3%) and 111 controls (10.0%).

Coloured Sweets.—At an estimated level of 12 oz. (340 g.) or more sweets per week there appeared to be an excess of cases (7.0%) over controls (4.4%), but this was balanced by an excess on the control side of children who usually ate between 3 and 12 oz. (85 and 340 g.) per week. As already shown, there was no deficiency of cases in the lowest consumption group.

Shop-fried Foods.—There was no difference in the proportion of cases and controls who had never had these foods, but consumption of fish and chips as often as once a week was reported by 191 cases and 140 controls. Once again the balance was made up by an excess of control children among those who occasionally had fish and chips.

In short, for none of the eight foodstuffs considered was there either a significant excess in the percentage of case children who had ever consumed them, or a consistent association between the amount consumed and subsequent events.

Other Factors

Contraception.—An attempt was made to discover whether there had been any attempt at family planning and if so what methods had been used. The proportion of completed records for contraception (89%) was lower than for most items, but the numbers of case and control mothers who gave satisfactory answers were similar (1,158 and 1,143). Chemical contraceptives were used by 124 case mothers (10.7% of those giving full information) and 107 control mothers (9.4%). The small difference arose principally in the leukaemia series, but these mothers did not differ significantly either from their own control pairs (P=approximately 0.21) or from the mothers of other cases (P= approximately 0.37).

Detergents.—The percentage of case mothers who stated that they used synthetic detergents was 61.3%—very similar to, but slightly below, the figure of 63.6% for mothers of controls.

Smoking.—Under this heading interviewers were asked to place the mother and father in one of the following categories: heavy, moderate, or light smokers, and non-smokers (the instructions gave quantitative definitions for these four categories). The figures quoted here relate only to "smokers" (at least one cigarette or pipe a day) and "non-smokers." The percentages of fathers and mothers in both series recorded as smokers were slightly higher than those recently reported for men and women of comparable age by Research Services Ltd. (Todd, 1957). For fathers of cases the proportion was 82.9% and for fathers of controls 80.9%, and for mothers 47.8% and 43.8% respectively. These percentages indicate a significant ($P \simeq 0.04$) excess among mothers of cases, but the difference is a small one (case/control ratio of 1.09), and we have not attempted to relate it to age, income, or number of children, as would be necessary before concluding that the mothers' smoking habits had affected their children. One factor which might well produce a genuine but irrelevant difference between mothers of cases and controls was, of course, the bereavement itself.

SECTION VII. FAMILY HISTORIES

Sibs—The records gave a complete tally of all the mothers' pregnancies up to the date of the interview, including those which ended with an abortion or stillbirth. As Table XXIV shows, there was no case/control difference in respect of stillbirths, but the case excess for abortions is at least suggestive, particularly as it is concentrated (like the case excess for threatened abortions during the "relevant" pregnancy) in the leukaemia series. The numbers of deaths among the liveborn sibs of the cases and controls were 132 and 129 respectively. This implies a very similar total mortality, since the numbers of liveborn sibs in the two series were almost equal (2,119 and 2,155) and the average number of years at risk was only slightly greater on the control side. Although most individual causes of death were equally common in the two series, deaths from malignant disease among the case sibs numbered eight as against only two for the controls. On the basis of the relatively high national mortality rates in 1953–5, and without allowing for reduction of the population at risk by other deaths, the expected number of deaths from malignant disease among the sibs of the cases is 2.15. It follows that the total of eight malignant deaths on the case side is significantly higher than expectation (P=0.001) (see Table XXV). Even five cancer deaths—that is, after the exclusion of three cases which were not certainly cancers—namely, the "acute anaemia," the "brain tumour," and the "growth in abdomen"—represent a significant case excess ($P<0.05$).

TABLE XXIV.—*Miscarriages and Stillbirths (Up to the Date of the Survey Child's Death)*

	Leukaemia		Other Cancers		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
Mothers reporting abortions ..	129	93	119	118	248	211
Total No. of abortions ..	173	122	153	156	326	278
Mothers reporting stillbirths ..	26	23	27	23	53	46
Total No. of stillbirths	26	28	32	25	58	53

TABLE XXV.—*Siblings of Cases With Death Attributed to Malignant Disease*

Serial No.	Index Case			Sibling		
	Sex	Diagnosis	Age at Death (Years)	Sex	Diagnosis	Age at Death (Years)
122	F	Lymphosarcoma ..	6	M	"Acute anaemia"	1
289	F	Acute lymphatic leukaemia	1	F	Leukaemia ..	1
290	F	Acute reticular leukaemia	0	F	,, ..	0
347	M	Acute lymphatic leukaemia	5	M	Generalized lymphosarcoma	3
				M	Retroperitoneal sarcoma	2
476	F	,, ,, ,,	5	M	"Brain tumour"	4
1293	F	Acute stem-cell leukaemia	1	F	"Growth in abdomen"	2
1656	M	Neuroblastoma ..	1	M	Lymphatic leukaemia	5

Parents.—One reason for not obtaining the first name on a control selection list was death of the mother; therefore little meaning attaches to the excess of dead parents in the case series (20) as compared with the controls (5). Among nine dead parents in the leukaemia series two had died of leukaemia and one of lymphosarcoma. Among 11 dead parents in the other cancer series four had died of some form of malignant disease. One of the five deaths among parents of control children was attributed to leukaemia and two to other malignant diseases.

Grandparents.—A total of 4,508 deaths of grandparents were reported. Judged by the proportions of deaths for which the cause was unknown or attributed to "senility," mothers gave better information about their own than about their husbands' parents, but there was no difference between the standard of information supplied by case and control mothers. Overall mortality was almost identical in the two series, the number of surviving grandparents being 2,936 in the case and 2,948 on the control side. Among 53 specified causes of death the largest proportional discrepancies between cases and controls were war injuries (60/95) and renal conditions (32/54), the excess in each case being on the control side. For malignant diseases as a whole there was a proportionally smaller but significant excess on the case side, the totals being 387 for cases and 316 for controls. This excess ran uniformly through the records (Table XXVI). The proportion of case children with an affected grandparent varied very little between the main diagnoses in the case series. There was no detectable variation in the sex ratio of cases as between groups with an affected grandparent on the paternal or maternal side, nor when these relatives were subdivided into father's father, father's

TABLE XXVI.—*Reports of Malignant Disease in Grandparents of Cases and Controls*

	Cases	Controls	Ratio
Grandparents of leukaemia series	172	140	1·23
,, of other malignant series	215	176	1·22
All paternal grandparents	186	152	1·22
All maternal ,,	201	164	1·23

mother, etc. One tabulation which did appear to show some variation was that of the reported site of the cancer in the grandparents. For example, lung cancers in grandparents showed *no* excess of cases over controls (52/55), but a relatively high case/control ratio was observed for breast and genital cancers (cases 58, controls 37).

Uncles and Aunts.—The total number of uncles and aunts was much the same for cases and controls (9,578 for cases, 9,425 for controls). Only deaths attributed to malignant disease were coded for these relatives, the numbers being: uncles and aunts of cases, 77; of controls, 55. The case/control ratio of 1.20 is almost identical with that for grandparents. In the case series there was no significant variation between the diagnostic subgroups, but the cancers in the uncles and aunts seemed to parallel two features noted in the grandparents. Thus cancers of the respiratory system showed no case excess (8/13), while breast and genital cancers showed a relatively large case excess (18/8).

Remoter Relatives.—Rather more case mothers volunteered statements about cancer in relatives beyond the second degree than control mothers, and this revealed one interesting cancer pedigree. This concerned a boy who died at the age of 6 from "cancer of the liver and bowel" and had five relatives on the father's side who had also died of bowel cancer—the father himself, the grandfather, the great-grandfather, and two aunts.

Consanguinity.—The number of cousin marriages in the case series was not large either in relation to the controls or in relation to the frequency in the general hospital population (Bell, 1940). Of the 10 consanguineous matings reported in the case series, only 5 (0.4%) were between first cousins. To these should be added one case (not fully followed up and not included in the 1,299 pairs) in which a father–daughter mating resulted in the birth of a girl who died at the age of 5 months from Letterer–Siwe's disease.

Discussion

All scientific investigations are faced with the problem of eliminating unknown bias from test and control observations. Where, as in the present case, the findings are based on human data and involve comparisons between facts which have been obtained by different observers from inexpert witnesses the main sources of such bias are: (1) unequal recording of events by different observers; (2) unequal reporting of events by the individuals chosen to represent case and control groups; and (3) faulty selection of cases and/or controls.

The first source of error has been controlled by insisting on the same doctor seeing each member of a given case/control pair. By so doing, errors due to lack of skill in interviewing and recording should be equally represented on the case and control sides. The same device might be expected to control the second source of error; but here we were on less certain ground, and have therefore applied other tests of reliability. Thus for several items specified in the questionaries the proportions of completed records in the two samples have been calculated and found to be alike. To illustrate this point we have summarized the findings for six items in which a low response rate might, with some justification, have been expected (Table XXVII). By these criteria it would seem that the doctors were equally pertinacious when questioning the cases and controls, and the mothers were equally helpful when replying to the doctors' questions.

TABLE XXVII.—*Response of Case and Control Mothers to Certain Questions*

Items	Response Rate (i.e., Percentage of Complete Answers)	
	Cases	Controls
Family income	87	88
Contraception	88	89
Dated illnesses (children)	89	87
,, (antibiotics and sulpha drugs) (children)	76	71
,, post-natal *x*-ray exposure	85	78
Specific cause of death (grandparents)	82	81

Other safeguards include repeated demonstration that significant differences between cases and controls are not compatible with any *general* tendency on the part of control mothers to be unduly forgetful or uncooperative. For instance, the case excess for two maternal diseases which might have affected foetal development—virus infections, and threatened abortions in the relevant pregnancy—were not accompanied by a case excess for other maternal illnesses, either during this period or previously. Again, the case excess for pulmonary diseases in childhood must be viewed against a background of almost equal numbers of all childhood diseases in the two groups, and the case excess for *x*-ray exposure in infancy against almost equal numbers for post-natal *x*-ray exposure as a whole.

The third source of bias—namely, faulty selection of cases and controls—has been dealt with in the following ways. The cases were drawn from the total number of cases for a three-year period, and those actually included in the survey represent such a high proportion of this total that, however atypical the *lost cases* may be, the consequences would remain numerically unimportant. The controls were drawn from the general population of surviving children, thus avoiding some of the confusion which might have resulted from using more accessible children—for example, other hospital patients, children attending welfare clinics, or siblings of cases. The controls actually included in the survey have been shown to differ in two important respects (first-born children and twins) from the national population. But because the numbers in these classes can be calculated from official vital statistics, it has been possible to show that the deficiencies in the control group had a negligible effect on the main finding—namely, a large excess for direct foetal irradiation in the case series. We have also shown that this finding was not affected either by systematic checking of the mother's statements against hospital records, or by the publication of a preliminary report half-way through the survey. Finally, we already know that at least one independent observer has tested this main finding and used different methods to obtain virtually the same result.

We are therefore confident that the finding in respect of direct foetal irradiation is not an artifact. Nor have we any reason to doubt that there are genuine case/control differences in other respects—namely, maternal age at the time of conception, post-natal pulmonary infections, and *x*-ray exposure in infancy. All these factors appear to have a "causal" association with childhood malignancies, but we do not suggest that any one of them is either a necessary or a sufficient cause of the malignant changes. The special risks associated with these events may perhaps be compared with the well-known risk of being a male child. Thus boys are known to run a higher risk than girls of developing cancers, but no one ever cites the Y-chromosome as a "cause" of cancer. Nor do we claim that any of the associations are quantitatively important. The number of childhood malignancies which they might account for is small even in relation to the recent increase of these deaths reported during the last two decades—about 60% for children under 5 years (see McKenzie, Case, and Pearson, 1957).

Summary and Conclusions

The pre-natal and post-natal experiences of a large group of children who recently died of malignant diseases have been compared, point by point, with the experiences of a similar group of live children.

The frequency of three pre-natal events—namely, direct foetal irradiation, virus infections and threatened abortion—was significantly higher among the dead children than among the live children.

One other pre-natal influence—namely, excessive maternal age—appears to increase the risk of leukaemia in childhood and to be related to the fact that this disease and mongolism tend to occur together.

The frequency of three post-natal events—namely, *x*-ray exposures in infancy, acute pulmonary infections and severe injuries—was significantly higher for children who subsequently died of leukaemia than for other children. In the "pre-antibiotic era" some of these children might have died before showing signs of the leukaemia.

The health of the mothers and the home background of the children were not significantly different in the two groups, but there were minor points of difference in the family histories of cancer and leukaemia.

Our final conclusions are that foetal irradiation does not account for the recent increase in childhood malignancies, but the finding of a case excess for this event does underline the need to use minimum doses for essential medical *x*-ray examinations and treatments.

A survey on the scale achieved could never have been contemplated without the active co-operation of doctors and health visitors too numerous to mention by name. Principal medical officers of health of local authority areas assumed responsibility for the field work of the investigation and completed the whole of their arduous and self-imposed task in the short space of 18 months. The interviews were done either by principal or by assistant medical officers of health, and health visitors did invaluable work in tracing cases and controls. We record with gratitude the high standard of the work in all regions.

We are also indebted to the Lady Tata Memorial Trust, which defrayed all costs other than those borne by the Health Departments and Oxford University; to the General Register Office, which provided essential data; to the Medical Research Council Working Party on Leukaemia, who gave us constant encouragement and advice; and to the mothers of the dead children, who had the courage to reopen a painful topic and so often expressed the hope that by doing so they might be helping other children.

Finally, we thank two members of our own staff: Miss Dawn Giles, who, while holding the Mary Goodger Research Scholarship, helped with the organization of the survey and the coding of records, and W. E. C. Brooksbank, who was responsible for the machine sorting of the data.

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DIET AND ARTERIAL DISEASE IN A POPULATION SAMPLE

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It is a curious paradox that one of the most hopeful features of ischaemic heart disease is the apparent rise in its clinical incidence (Ryle and Russell, 1949; Morris, 1951); for it is this rise, especially as it affects the middle-aged, which suggests the importance of environmental factors rather than simple ageing. This raises the hope that if only the responsible change can be identified its reversal may possibly prevent or even cure the disease. Unfortunately, however, the search for the relevant change is impeded by the complexity of social development. For instance, the apparent fall in the mortality from ischaemic heart disease which Malmros (1950) observed in some Scandinavian countries during the last war, and which he attributed to the effects of food rationing, might have been due to some other of the many profound effects of war upon society.

Other attempts to correlate diet with the clinical or necropsy incidence of ischaemic heart disease in different populations are all open to similar criticism, since the various races that were studied differed in many ways besides diet (for example, Keys *et al.*, 1954a, 1954b; Bronte-Stewart *et al.*, 1955; see Yudkin, 1957). A more direct approach is to compare, within the same population group, those with and without the disease. This method has been used in comparing hospital cases with unaffected hospital patients, or else with healthy volunteers (for example, Gertler, White, *et al.*, 1954). Such studies are open to the serious objection that patients and controls come from different population groups. The proper control for a man in hospital with ischaemic heart disease is a man taken at random from the same population group; such ideal control is almost impossible of achievement.

An investigation requiring a completely acceptable control group is more suitably based upon the population at large. Such an approach is most laborious, for, in order to find a small number of people with the disease from among the general population, it is necessary to interview and examine a much larger number. In addition, those discovered may have only a limited desire to co-operate. In the present study these problems were simplified by making use of material which had been collected for a different purpose, but which was also very suitable for a controlled study of diet and arterial disease. Our purpose was to determine whether, within a defined section of the general population, the diet of those who had clinical ischaemic heart disease or intermittent claudication differed from those who had not.

Methods

In 1953–4 one of us collected data for a study on the inheritance of diabetes mellitus. The names and addresses were obtained of all first-degree relatives of (*a*) 550 diabetics

attending hospital, and (*b*) 520 patients attending the skin, minor surgical, and general medical clinics. These relatives were invited to attend the hospital for interview and examination, when specific questions were put regarding, *inter alia*, symptoms of arterial disease. This information provided the material for the present survey.

From each of the two groups of relatives was collected a group of "atheromatous" patients, consisting of those who gave a history of angina pectoris, cardiac infarction, or intermittent claudication; in each instance the last was supported by the absence of one or more ankle pulses. Each "atheromatous" subject was matched by the next person of the same age (± 3 years) and sex who gave no history of these symptoms. These "less atheromatous" subjects formed the control group. Persons over the age of 65 were excluded, as also were diabetics. Jewish subjects were matched by Jewish controls. All subjects were of British nationality.

The selected subjects in the atheromatous and control groups were each sent a letter in which they were asked to say if they were willing to answer questionaries about their diet, and also to state their occupation in the past 10 years, and whether or not they were taking any special diet. When a control subject could not be traced or would not agree to take part, a letter was sent instead to the next suitable person on the list. The subjects eventually studied comprised 7 pairs of relatives of diabetics and 17 pairs of relatives of non-diabetics. The atheromatous group consisted of 5 subjects (3 men and 2 women) with a history of cardiac infarction, 14 subjects (4 men and 10 women) with angina pectoris only, and 5 subjects (3 men and 2 women) with intermittent claudication only.

The assessment of the diet was based on answers to questionaries sent through the post, each questionary dealing with one day's food. All the common foods that might be eaten at each meal were listed, together with space for the insertion of any other dishes. The subject was asked to mark against each dish the quantity that was eaten; the measures specified on the questionaries were homely rather than scientific—for example, for porridge, the number of tablespoonfuls; and for butter, whether "thick," "thin," or "average." At the end of each sheet was the question, "How much did you smoke during the day?"

The questionaries and instructions were identical for both the atheromatous and the control group. No suggestion was made that fat, or any other food, was regarded as of special importance. All subjects were led to believe that they were being studied as members of the healthy population. Fourteen pairs of subjects were questioned in the months of November and December, and the remainder in April and May.

Each subject initially received two questionaries without prior notice on a Monday morning. The first related to the diet of the previous day, and had to be filled in from memory; the second dealt with the diet for Tuesday. This arrangement was adopted so that the first questionary would be free from bias due to changes in diet introduced because the subject knew he or she was being questioned, and so that the second questionary would be more or less free from bias due to faulty memory.

A second pair of questionaries was posted one to three weeks after the first, again without prior notice. The posting day was determined randomly, and again one questionary was retrospective and the other prospective. The members of each pair of subjects received their questionaries simultaneously.

The food content of the diets was calculated from the completed questionaries, using the food tables of McCance and Widdowson (1946) for the carbohydrate, protein, and fat content of prepared dishes, and data provided by Hilditch (1956) for the fatty-acid composition of the fats. In order to allow for the differences in diet between Sundays and weekdays, each subject's intake was calculated first for a whole week, and the daily means were derived from this. For convenience, the values for total fat have been broken down in the proportions of their constituent fatty acids: the resulting figures are in a measure misleading, since natural glycerides are always mixed. The fatty acids were grouped as saturated, mono-ethenoid, and poly-ethenoid (including di-ethenoid); they were also separately grouped into those with a chain length of 18 or more carbon atoms, and those with shorter chains.

Results

In the atheromatous group both men and women were on average slightly older than their controls, the mean difference being 0.54 year (Table I). Body measurements showed the atheromatous subjects to be a little shorter and a little heavier than the controls. The atheromatous men were on average 11.2 lb. (5.1 kg.) below their highest known weight, as compared with 8.1 lb. (3.7 kg.) for the controls. For the women the differences were 6.8 and 7.8 lb. (3.1 and 3.5 kg.) respectively.

Since the atheromatous subjects were on average slightly heavier than the controls, it is necessary to consider how far this might affect their calorie intake. The relation between calorie intake and body weight for the two groups was therefore studied (Table II), and it was found that there

TABLE II.—*Relation Between Calories and Body Weight for Males*

Body Weight (lb.)		Mean Daily Calories
lb.	kg.	
110–	49·9	2,330
130–	58·9	2,680
150–	68·0	2,870
170 and over	77·1 +	1,980

TABLE I.—*Comparison of Age, Bodily Measurements, and Diet in Atheromatous and Control Subjects*

	Males			Females			Total			
	A	C	A–C	A	C	A–C	A	C	A–C	P
Age (years)	56·60	55·90	+0·70	56·57	56·14	+0·43	56·58	56·04	+0·54	0·1 0·2
Height (in.)	65·30	66·00	−0·70	62·43	62·93	−0·50	63·63	64·21	−0·58	0·02 0·05
Weight (lb.)	153·9	146·9	+7·0	155·2	152·3	+2·9	154·7	150·1	+4·6	0·5 0·6
Highest known wt. (lb.)	165·1	155·0	+10·1	162·0	160·1	+1·9	163·2	158·1	+5·1	0·5 0·6
Calories/day	2,800	2,259	+541	1,856	1,697	+159	2,249	1,931	+318	0·05 0·1
Carbohydrate (g./day)	329·9	274·5	+55·4	211·5	209·6	+1·9	260·8	236·7	+24·1	0·3 0·4
,, (% cals.)	48·3	49·7	−1·4	46·7	50·6	−3·9	47·5	50·3	−2·8	0·1/0·2
Protein (g./day)	83·3	66·2	+17·1	57·8	56·7	+1·1	68·4	60·6	+7·8	0·1/0·2
,, (% cals.)	12·2	12·0	+0·2	12·8	13·7	−0·9	12·5	12·8	−0·3	0·7 0·8
Fat (g./day)	119·0	92·9	+26·1	80·8	65·2	+15·6	96·7	76·7	+20·0	0·02 0·05
,, (% cals.)	39·5	38·3	+1·2	40·5	35·7	+4·8	40·0	36·9	+3·1	0·05 0·1
Satd. fat (g./day)	65·5	49·3	+16·2	43·0	36·2	+6·8	52·3	41·6	+10·7	0·001/0·01
,, (% fat)	54·9	53·2	+1·7	53·3	55·5	−2·2	54·1	54·3	−0·2	0·4/0·5
Mono-eth. fat (g./day)	45·2	36·4	+8·8	32·2	24·6	+7·6	37·6	29·5	+8·1	0·02/0·05
,, (% fat)	38·1	39·1	−1·0	39·8	37·6	+2·2	38·8	38·4	+0·4	0·2/0·3
Poly-eth. fat (g./day)	8·3	7·2	+1·1	5·6	4·4	+1·2	6·8	5·6	+1·2	0·05 0·1
,, (% fat)	7·0	7·7	−0·7	6·9	6·9	0·0	7·0	7·3	−0·3	0·2/0·3
Short-chain fat (g./day)	48·8	38·3	+10·5	33·4	27·3	+6·1	40·0	32·1	+7·9	0·02 0·05
,, (% fat)	41·0	41·3	−0·3	41·5	42·1	−0·6	41·3	41·8	−0·5	0·5 0·6

A = Atheromatous group. C = Control group. P = Probability.

was only a slight tendency for calorie intake to increase with body weight; in fact, in each sex the calorie intake fell off in the highest-weight group.

Dietary analysis showed not only significant differences between the atheromatous and control groups as a whole, but also discrepancies between these differences for men and women. Broadly speaking, the atheromatous men were much bigger all-round eaters than their controls, whereas the atheromatous women were bigger eaters of fat only. None of the atheromatous subjects was taking a special diet because of his or her disease.

The atheromatous males' calorie intake was 24% higher than that of their controls, and the likelihood of such a difference arising by chance is less than 1 in 100. Their mean consumption of carbohydrate was 20% greater ($P<0.01$), of protein 26% ($P<0.2$), and of fat 28% ($P<0.2$). The lesser degree of significance for the intakes of protein and fat was due to a wider scatter of the observations. Study of the percentage contributions of the various foodstuffs to the total calories showed only trivial differences between atheromatous subjects and controls.

In the case of the women, the atheromatous subjects still showed a higher calorie intake; but the excess (9%) was much smaller than for the men, and did not achieve the 1 in 20 level of significance. For carbohydrate and protein intake there was almost no difference at all; that is to say, the excess of calories was derived almost entirely from fat. Their excess fat consumption (24% more than the controls') was not itself significant, but the proportion of calories taken as fat was significantly increased (40.5% as compared with 35.7%, $P<0.05$). However, the combined data for the two sexes showed a significantly higher fat intake in the atheromatous group ($P<0.05$); and since the trends for the two sexes were similar, it is quite possible that these might each have achieved significance if more observations had been available.

When the figures for total fat intake are broken down in the proportion of their constituent saturated and unsaturated fatty acids, it may be seen that the atheromatous men ate an absolute excess of all fractions, as compared with their controls; this is not surprising, in view of their large total fat intake. They consumed, however, a rather higher proportion of their fat in a saturated form, and a correspondingly lower proportion as di- and poly-ethenoid fatty acids; the difference did not reach significance. Rather surprisingly the atheromatous women took proportionately less of their fat in a saturated form as compared with their controls. Although the excess of saturated fat in the atheromatous group achieved a probability of only 0.05–0.1 for each of the two sexes separately, the combined data for both sexes achieved a significance level of less than 1 in 100.

James *et al.* (1957) have put forward the hypothesis that the chain length of fatty acids may be more important than their saturation in relation to atheroma. Their suggestion implies that the short-chain fatty acids (contained in highest proportion in milk fat) may be atheroma-producing, whereas the long-chain acids (contained in highest proportions in most vegetable oils) may be atheroma-sparing; most animal fats occupy an intermediate position. Since vegetable oils make only a fairly small contribution to fat intake in this country, the problem resolves itself mainly into the relative amounts of milk fat and animal fat in the diet.

In the present analysis fatty acids have been grouped according to chain length into those with 18 or more carbon atoms, and those with 16 or less. Figures for the latter are included in Table I. The percentage contribution of short-chain fatty acids to total fat intake was very similar in the two groups, and hence the differences between the groups in absolute figures follow the same pattern as for total fat intake. There was no evidence to suggest that chain length possessed any peculiar importance.

In an attempt to assess some of the errors attaching to this type of dietary survey it was arranged that half the questionaries should be retrospective and half prospective. The results obtained from these two sets of questionaries have been compared. For carbohydrate intake the retrospective questionaries gave a mean daily intake for all subjects of 254.0 g. for weekdays and 267.2 g. for Sundays; the figures from the prospective questionaries were 251.0 g. and 270.8 g. respectively. These differences were not significant.

The subjects' occupations are summarized in Table III. The pattern was very similar in each group, both with regard to the likely expenditure of physical energy and

TABLE III.—*Occupational Distribution*

	Occupation	No. of Subjects	
		Atheromatous	Control
Male	Sedentary or clerical	4	3
	Light engineering	3	3
	Boot repairer	1	0
	Painter and decorator	1	0
	Warehouseman	0	1
	Barrow boy	0	1
	Lorry driver	0	1
	Retired	1	1
Female	Housewife	11	12
	Clerical	1	2
	Industrial cleaner	1	0
	Canteen assistant	1	0

(so far as could be ascertained) with regard to probable income. Apart from one retirement in each group, no change of occupation had occurred within the previous 10 years.

All subjects were also asked to give details of any physical exercise or active hobbies undertaken apart from their occupations, and, in the case of the employed, the distance walked on the way to work each day. The mean distance walked to and from work each day was 0.95 mile in the atheromatous group, as against 3.1 miles in the control group. Of the atheromatous subjects, only five reported active hobbies (gardening or odd jobs); these occupied them on average for 8.6 hours weekly. Seven of the control subjects reported active hobbies, with a mean of 10.9 hours weekly.

Each questionary also included a question on the amount smoked during the day. Data from the answers are presented in Table IV; the results are expressed as grammes of tobacco per day (Doll and Hill, 1954). They show only trivial differences between the atheromatous and control groups.

TABLE IV.—*Smoking Habits*

Amount of Tobacco Consumed per Day (g.)	No. of Subjects			
	Atheromatous		Control	
	Men	Women	Men	Women
0	2	11	3	11
1–10	3	3	3	2
11–20	3	0	3	1
21–30	1	0	0	0
Not stated	1	0	1	0

Discussion

The division into atheromatous and control groups on the basis of a clinical history taken two to three years previously may be false or misleading in a number of ways. For example, the original history may have been erroneously interpreted; some control subjects may have developed evidence of atheroma since their history was taken; and others, though without symptoms, may yet have a dangerous degree of atheroma. Nevertheless it is indisputable that the two groups represent, respectively, a greater and a less severe degree of the disease, and the possible presence of the disease in the controls only enhances the significance of any differences found.

The method of dietary inquiry used in this study is new, and must therefore be examined critically. Errors may have been introduced through lack of understanding of the

questionaries, the wide interpretations that could be placed on the homely food measures employed, faulty memory, or changes in diet introduced because the subjects knew that they were being questioned. The similarity of results obtained from retrospective and prospective questionaries suggests that the last two of these were probably not of major significance. In addition, the tables of food values on which the analysis was based are certainly only approximate. All errors, however, were equally apt to occur in each of the two groups: for identical questionaries were sent to all subjects, and members of control and atheromatous groups alike believed themselves selected as typical members of the general population. It follows that, even if the errors were great, they are irrelevant to the significance of differences between the two groups. There remains the possibility that, through superior intellect or temperament, the members of the atheromatous group were less likely to omit information when completing the questionaries. This possibility cannot be disproved; but there was no evidence for it, and it is a criticism that can be levelled at any type of dietary survey.

The investigation has shown a number of significant differences in diet between the atheromatous and control groups, but their interpretation is difficult. It may be that highly significant differences in the intake of one foodstuff may be of no aetiological importance, but have arisen because they were linked with other differences in diet or way of life that are important. Owing to large random variations and the smallness of the series, it may be that factors of less statistical significance may be of greater aetiological significance; and other differences that in this survey have failed to reach any acceptable level of significance might in a larger series be shown to be important. Similarly, the degree of significance of some of the results might have been less in a larger series.

Despite the well-known difference in the sex incidence of ischaemic heart disease and intermittent claudication, little attention has been paid to the possibility that this might reflect differences in diet (see Keys, 1956). Field and laboratory studies have dealt almost exclusively with males, and reports of mortality trends have usually presented only combined data for both sexes. In some instances, such as calorie intake, the sexes showed similar trends, but the differences were greater in one sex. In other instances, however, the two sexes behaved quite differently. To take an extreme example, the percentage contribution of the mono-ethenoid fat fraction to total calorie intake was identical for atheromatous and control males, whereas the two female groups showed a difference of 2.6% ($P<0.01$). It must, however, be pointed out that a history of angina pectoris but not of infarction was given by 10 of the 14 women, but by only 4 of the 10 men. Thus the difference in diet may really represent, not differences between the sexes, but differences between cardiac infarction and angina pectoris.

The chief characteristic of the atheromatous men was that their calorie intake was 24% higher than that of their controls: expressed mechanically, their bodies appeared to be less efficient machines. In the attainment of this higher intake they showed little preference for any particular foodstuff as compared with the controls; hence there were no significant differences between the two groups as regards the respective percentage contributions to total calories of carbohydrate, protein, and fat. In absolute figures, the biggest percentage excess related to fat; but there was a fairly wide scatter of the differences between individual pairs of subjects, and the mean difference did not reach the 5% significance level. An excess carbohydrate intake, on the other hand, was more constant, and the difference between the two groups was highly significant.

The problem is not much clarified by other reports. The fall in mortality from ischaemic heart disease in certain Scandinavian countries during the war (Malmros, 1950; Strøm and Jensen, 1951), which was associated with a fall in fat consumption, was associated also with a fall in total calories. The comparisons between native and white populations in South Africa (Bronte-Stewart *et al.*, 1955) do not offer any data on calorie intake. The studies of Keys *et al.* (1952, 1954a, 1954b) on samples of the populations of Minnesota, Naples, and Madrid included estimates of calorie intake; but these should probably be interpreted with caution, since members of such widely differing populations might also vary in their ability to provide accurate answers to dietary questionaries. The evidence from the present survey, if viewed in isolation, would tend to incriminate either a high total calorie intake or a high carbohydrate intake, rather than a high fat intake or a high proportion of calories eaten as fat.

Comparison of the atheromatous and control women showed (by contrast with the men) only a slightly higher calorie intake in the atheromatous group; but the proportion of calories taken as fat was significantly greater. In the combined data for the two sexes the excess in total fat intake of the atheromatous subjects achieved significance at the 5% level.

It has been suggested that atheroma may be aggravated by a relatively high intake of saturated or animal fat, or by a deficiency of unsaturated fatty acids (Kinsell *et al.*, 1952, 1953; Ahrens *et al.*, 1954; Beveridge *et al.*, 1955; Bronte-Stewart *et al.*, 1956; Sinclair, 1956). The present results do not favour the importance either of an absolute deficiency of unsaturated fatty acids or of a high relative proportion of saturated to unsaturated fatty acids. They are, however, consistent with the possible importance of a high total intake of saturated fatty acids.

Summary

The diet has been studied of (*a*) 10 male and 14 female subjects with atheromatous disease, and (*b*) the same number of randomly selected control subjects, each pair being matched for age and sex. Figures for the atheromatous group showed a higher intake of each of the main foodstuffs. Statistically, the most significant differences related to total calories and carbohydrate among the men, and to saturated fat for both sexes. The excess in total fat intake also reached significance at the 5% level. The data did not provide any evidence to incriminate any deficiency of unsaturated or long-chain fatty acids as an important aetiological factor.

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ASPIRATION IN THE TREATMENT OF PRIMARY TUBERCULOUS PLEURAL EFFUSION

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One of the after-effects of primary tuberculous effusion is persistent pleural thickening, which may be slight and manifested by a radiological abnormality only, or so marked as to cause deformity of the thoracic cage and scoliosis of the spine.

Whatever its degree, pleural thickening is likely to result in impaired pulmonary function, and even those cases which show minimal *x*-ray changes, or none at all, may still show some impairment of lung function due to the pleural symphysis which has occurred.

What has been termed an "active" form of treatment, consisting of repeated aspiration of the pleural cavity, together with postural treatment and physiotherapy, has been suggested by Birath (1952) and Mackay-Dick and Rothnie (1954) as a method of reducing the incidence of pleural thickening after pleural effusions. Mackay-Dick and Rothnie claimed that not only was the incidence of thickening reduced but also that patients on this form of treatment fared better in the early stages than those not so treated, in that they felt better, looked better, and ate better, and their fever subsided more rapidly.

There are, however, disadvantages associated with aspiration of the pleural cavity. Thus Pagel, Simmonds, and Macdonald (1953) pointed out that puncture of the pleura may excite further exudation of fluid, and Emerson (1955) found that the E.S.R. rose and fluid reaccumulated after therapeutic aspiration. Robson (1952) stressed the danger of pulmonary oedema occurring if much fluid is removed quickly at one time, and Hudson (1957) stated that, other things being equal, fluid should not be removed, because of its high antibody content. It has also been said that the "natural splintage" of the lung afforded by the fluid should not be upset by aspirating it. Until recently, the general consensus of opinion has been in favour of not aspirating pleural effusions except for diagnosis, for the relief of dyspnoea or pressure symptoms, or for the removal of a small amount of fluid when the effusion has persisted for some weeks (Mackenzie, 1952; Pagel *et al.*, 1953).

It seemed to us that, although good results had been obtained with the "active" form of treatment advocated by Mackay-Dick and Rothnie, the place in it of repeated aspiration was still in doubt, and in view of the possible disadvantages associated with aspiration we felt that this aspect of treatment required further study. Accordingly, we carried out a trial in which the results of treatment were compared in two groups of patients, one receiving repeated aspirations and the other no further aspiration after that for diagnosis. Fifty-two patients were included in the trial, all of whom were soldiers aged 17–24 who developed primary tuberculous pleural effusion during their Army service. All were admitted to the Connaught Hospital (Army Chest Centre) between October, 1955, and November, 1956.

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Diagnosis

Each patient had postero-anterior and lateral radiographs taken on admission. Tomography was carried out later on every case. Parenchymal lesions, typical of primary foci, were noted in four patients. The other 48 had no radiological evidence of parenchymal disease throughout the period of the trial. No instance of effusion secondary to adult-type tuberculosis was included in the series.

The diagnosis of primary tuberculous effusion was based on three main findings. (1) Typical onset and course, with the absence clinically and radiologically of other possible causes of effusion such as pneumonia, upper respiratory infection, emboli, bronchiectasis, or trauma. (2) Positive Mantoux or Heaf reactions. Six patients were Heaf-positive grade 3. The remaining 46 were all Mantoux-positive, 27 of them to 1/10,000 old tuberculin (1 T.U.). (3) Examination of pleural aspirate, which was performed on every patient. Only those showing the typical straw-coloured predominantly lymphocytic fluid which was sterile on culture for pyogenic organisms were included. Direct film examination of pleural fluid and sputum for tubercle bacilli was carried out on every case, but not all cases transferred from other hospitals had had culture or guinea-pig inoculation techniques applied. Of the 52 cases, pleural fluid culture was positive in six cases and guinea-pig inoculation positive in three. No positive findings were reported from sputum, laryngeal swabs, or gastric washings.

Routine Treatment Common to all Patients

The standard treatment consisted of streptomycin, 1 g. daily, and isoniazid, 100 mg. twice daily, this regime being continued until 100 g. had been given, when the dose was reduced to 1 g. on alternate days with continued daily isoniazid. A total of 140 to 150 g. of streptomycin was usually reached during treatment. Three patients had started treatment with P.A.S. instead of isoniazid before admission; they were continued on this regime. Vitamins A, D, and B complex and ferrous sulphate were given throughout treatment. Bed rest was continued for three months in every case. Those patients still showing pyrexia or a raised erythrocyte sedimentation rate at the end of this time were treated on further bed rest until these had subsided. Upgrading occupied a further three months, by the end of which time patients were up to all meals and had carried out graduated walking exercises. Breathing exercises directed to the improvement on the affected side of diaphragmatic and chest-wall movement were carried out by all patients; these were begun when the temperature had become normal. Patients were encouraged to spend rest periods, each of an hour twice a day, lying with the unaffected side arched over a pillow, in an endeavour to stretch the affected side and prevent rib-crowding. This regime was applied to all patients who completed their treatment at the Army Chest Centre.

Thirteen patients in this series were transferred to other sanatoria during treatment, but none before aspiration therapy had been completed and their temperatures and E.S.R.s had returned to normal. Their radiographs at the six months' stage were made available to us by the chest physicians concerned. The main difference between these patients and those remaining at this hospital for the whole of the follow-up period occurred in the type of chemotherapy they received. Both the drugs used and the dosage schemes employed varied to some extent from our practice. Of the 13 patients concerned, however, all received streptomycin, and the total dose after six months' treatment varied between 84 and 180 g., the average being 153 g.

Aspiration Technique

All patients with pleural effusions were subjected to an initial diagnostic aspiration of not more than 100 ml. Thereafter, those patients admitted to the series were either not aspirated again (these comprised group A) or they were aspirated repeatedly (group B). In the latter, as much fluid as possible (but not more than 2 pints—1,140 ml.) was removed on the first occasion, and aspiration was repeated (normally on successive days) until no more fluid could be obtained. In a few patients aspiration was repeated on alternate days or on every third day, but never less frequently than that.

Aspiration technique followed normal practice. The site of aspiration was determined clinically and radiologically. After local analgesia, fluid was removed through a 13 s.w.g. needle by a 30-ml. syringe fitted with a two-way tap.

In group B, 1 g. of streptomycin in 10 ml. of water was instilled into the pleural cavity after each aspiration. This was the only difference in chemotherapy between the groups. In group A failure of the fluid to absorb spontaneously after a period of one month was regarded as an indication for therapeutic aspiration, and this was carried out on three patients in the group.

Allocation of Patients to Groups

Patients were allocated to one or other of the two groups as follows. Those who were admitted direct to this hospital were placed alternately in one group or the other as they were admitted, and treatment was continued accordingly. Patients transferred from other hospitals and already under treatment were allocated to one group or the other according to whether their previous treatments had been by single diagnostic or repeated aspiration.

Certain patients admitted with pleural effusion from other hospitals had to be excluded from the series because their aspiration or drug regimes had not been in accordance with those practised at this centre; there were 21 of these. Otherwise, every case of pleural effusion admitted between October, 1955, and November, 1956, which satisfied the diagnostic criteria indicated above, was included in the series.

Comparison of Groups

Group A, treated by single aspiration, comprised 19 patients. Of these, seven were admitted to this hospital within a few days of onset of symptoms, and were allocated by the alternate admission method. The remaining 12 had begun treatment elsewhere, but their diagnosis and treatment fulfilled the criteria for admission to the series. Group B, treated by repeated aspirations, comprised 33 patients, eight admitted direct and 25 secondarily.

Table I shows the number in each group divided according to the maximum effusion size, in which there was no significant difference between the groups. The size of the effusion was estimated from the radiographic appearance as follows: large if the bulk of the fluid extended above a horizontal line through the lower border of the second rib anteriorly; medium if above a similar line through the fourth rib; and small if below this line. Thin lateral prolongations of fluid above the main bulk of the effusion were discounted.

TABLE I

Effusion Size:	Small	Medium	Large	Total
Group A	5	9	5	19
,, B	10	14	9	33

Table II shows initial similarities between the groups as regards mean E.S.R., Mantoux state, and positivity of pleural fluid and sputum. The groups were similar also as regards age, sex, and treatment received (other than the aspiration regime).

TABLE II

	Group A	Group B
Initial mean E.S.R.	34·2 ± 9·6	37·5 ± 11·2
Mantoux-positive at 1 T.U.	10 (53%)	17 (52%)
Findings of *M. tuberculosis*	3 (16%)	6 (18%)

As some of these patients began treatment in other hospitals before being transferred to this centre it might be thought that differences in aspiration technique would introduce differences between the groups. However, we found that those patients admitted primarily to this centre, to whom this objection could not apply, showed results similar to those obtained from the series as a whole. Furthermore, those patients whose initial treatment differed from our own practice were excluded from the trial.

In each group, two patients showed on *x*-ray examination parenchymal lesions which were considered to be primary foci. No complications occurred in group A, but therapeutic aspiration was carried out once on three patients in the group who had failed to show any spontaneous absorption of fluid after one month's treatment. The only complication which occurred in group B was one small pneumothorax, following aspiration, which had absorbed completely after eight weeks and which required no treatment.

The number of aspirations performed in Group B is shown in Table III. The average number of aspirations performed on each patient was 4.2. The majority (17) of the patients had three aspirations.

TABLE III

No. of aspirations	2	3	4	5	6	7	8	9
,, ,, patients	3	17	3	2	3	—	3	2

Assessment of Progress

Progress was assessed on the length of time the temperature and E.S.R. remained raised, the radiological appearance after six months' treatment, and the duration of the effusions.

Duration of Raised Temperature.—Twice-daily recordings were available in all but five cases. Patients were regarded as apyrexial when their temperature remained consistently below 99° F. (37.2° C.). It was found that the temperature fell to normal in group A in a mean of 30.4 ± 8.2 days from the date of the first aspiration, and in group B in a mean of 30.2 ± 16.2 days. This difference is small, but it is a significant one having regard to the standard deviations. The longest duration of pyrexia in group A was 42 days and in group B 80 days. The three patients in Group A who required therapeutic aspiration showed no rise in temperature after their aspirations.

TABLE IV.—*Mean E.S.R.*

	Weeks After First Aspiration										
	0	1	2	3	4	5	6	7	8	9	10
Group A	34·2	35·1	25·0	21·3	20·0	15·8	15·2	11·1	7·9		
,, B	37·5	40·0	40·0	36·1	32·0	28·8	24·3	24·5	20·0	15·8	9·1

Duration of Raised E.S.R.—The E.S.R. was recorded weekly until it had remained normal on three consecutive occasions. Thereafter it was estimated monthly. The E.S.R. was regarded as normal when it was below 10 mm. in one hour (Westergren). Table IV shows that the mean E.S.R. fell to normal in group A in eight weeks and in group B in 10 weeks, measured from the date of first aspiration. Two of the three patients in group A who required therapeutic aspirations showed a marked rise in E.S.R. after re-aspiration.

Degree of Residual Opacity after 6 Months' Treatment.—Radiographs taken six months (plus or minus three

weeks) after treatment was begun were reviewed and residual opacities assessed as follows: First-degree opacity was when not more than the costophrenic angle was obliterated and there was no diaphragmatic elevation or tenting; third-degree opacity was when there was thickening, rib-crowding, and scoliosis of a degree meriting consideration for decortication; second-degree opacity comprised all intermediate cases. The results are shown in Table V. It will be seen

TABLE V.—*Degree of Opacity After 6 Months' Treatment*

Degree:	1	2	3
Group A (19 cases)	14 (73·7%)	5 (26·3%)	—
,, B (33 ,,)	21 (63·6%)	11 (33·3%)	1 (3·1%)

that 73.7% of group A and 63.6% of group B either had no thickening at all or at most showed minimal changes consisting of an obliterated costophrenic angle only, without diaphragmatic elevation or tenting. These patients are regarded as having made satisfactory progress. Patients having moderate or severe pleural thickening after six months' observation comprised 26.3% of group A and 36.4% of group B. The difference is not statistically significant having regard to the number of patients in each group.

Duration of Effusion.—Every patient was radiographed on admission, and this was repeated monthly, or more often if fluid was absorbing rapidly. A clinical impression was gained that, while repeated aspiration often resulted in an early rapid reduction in effusion size, residual pleural thickening was often marked and cleared slowly; in group A, fluid seemed to clear more completely once resorption had begun. This impression was confirmed when the rates of clearing in the two groups were compared (Table VI).

TABLE VI.—*Patients Showing More than First-degree Opacity*

	Months of Treatment from Date of First Aspiration											
	1		2		3		4		5		6	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Group A	14	73·7	12	63·2	7	36·8	6	31·6	5	26·3	5	26·3
,, B	22	66·6	14	42·4	13	39·4	12	36·4	12	36·4	12	36·4

Discussion

This trial on a small series of primary tuberculous pleural effusions shows that in the repeated-aspiration group of cases the E.S.R. declined more slowly than in the single-aspiration group, whilst the temperature fell slightly more quickly.

The effect of repeated aspiration in prolonging the duration of an elevated E.S.R. was commented on by Emerson (1955), but it is important to remember that in our series the comparison is between single aspiration on the one hand and repeated aspiration with intrapleural streptomycin on the other.

The slightly more rapid fall of temperature in our repeated-aspiration group confirms the findings of Mackay-Dick and Rothnie (1954), although we found the advantage in this respect of that group over the single-aspiration group to be small.

So far as the rate of clearing is concerned, our conclusion is that effusions treated by repeated aspiration tend to clear more rapidly in the early stages than those left to absorb spontaneously, but by the six-months stage there is little difference in the amount of residual pleural opacity.

Insufficient time has elapsed for a conclusion to be reached on the effect of repeated aspiration on the incidence of subsequent tuberculosis, but during the six-months follow-up period no patients in either group developed fresh evidence of tuberculosis.

Aspiration of the pleural cavity causes the patient some discomfort and may give rise to complications; it should not, therefore, be performed unnecessarily. Although our results show little apparent advantage in repeated aspirations, we formed the clinical impression that many patients, especially those with large effusions, felt better if their effusions were aspirated early on, even although this subjective improvement was not matched by objective criteria; in view of this we felt that a compromise between the two methods might prove the ideal form of treatment—that is, an initial large aspiration (at the time of the diagnostic one) and no aspiration thereafter.

It had originally been our intention to include in the trial a third group of patients who had one large initial aspiration performed at the time of diagnostic aspiration and who were not aspirated further, but we had insufficient cases to include this group in the series. The results in those patients who were treated in this way were good, however, and during the past eight months this method has been our standard practice. Later, it is hoped to collect similar data on this group for comparison with the results of the present trial.

Summary

A comparison has been made between the use of single and repeated aspiration in the treatment of primary tuberculous pleural effusion.

Of the 52 patients included in the trial, 33 were treated by repeated aspiration and 19 by single diagnostic aspiration.

The results were compared in terms of duration of pyrexia, and elevated E.S.R., rate of clearing of effusion, and residual opacity after six months' treatment.

There was a slightly shorter duration of pyrexia and a prolonged duration of raised E.S.R. in the repeated-aspiration group.

Although the repeated-aspiration group tended to clear rapidly in the early stages, there was no significant difference between the groups in the amount of pleural opacity remaining at six months.

Our thanks are due to Dr. E. Lewis Faning for his advice on the setting out of the statistical material and to Sergeant E. F. West, R.A.M.C., for typing these notes for us.

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The Tobacco Manufacturers' Standing Committee, in its report for the year ended May 31 last, states that experiments have been carried out in the industry's laboratories to find substances that might be used to reduce the minute quantities of benzpyrene in cigarette smoke. Two such substances have been found—copper nitrate and platinum diamminonitrite. An earlier claim that the addition of 4% ammonium sulphamate to cigarette paper has a similar reducing effect was not substantiated, though the addition of relatively large amounts of ammonium sulphamate to the tobacco itself did reduce the benzpyrene content of the smoke. Besides benzpyrene a number of other polycyclic hydrocarbons have been found in cigarette smoke, and they are being investigated. Tests continue to show that, since the virtual elimination of the use of arsenical insecticidal sprays on tobacco crops, traces of arsenic have almost disappeared from cigarettes made in Britain. A new research project is to be the study of the principles of "smouldering combustion, particularly in relation to forced air supply in products such as tobacco." The report may be obtained from the committee's offices, 6–10, Bruton Street, London, W.1.

DEPRIVATION OF PARENTS DURING CHILDHOOD

ITS FREQUENCY IN SOME CONTEMPORARY YOUNG SERVICE MEN

BY

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The statistics presented below are offered not only because of differences which are apparent between the diagnostic groups but in the belief that they may serve as a background against which to assess the stress to be laid on a history of separation from a parent.

Bowlby (1951) reviewed the evidence pointing to the very frequent history of separation of the child from the parents in those with behaviour disorders. He regretted the paucity of controlled series in the case of psychiatric patients. An American study by Oltman *et al.* (1952) would appear to meet this objection, though a comparable controlled series from this country does not seem to have been reported.

Among the statistics reported below, some relate to patients with a history of head injury. A number of workers have claimed that accident-prone persons tend to come from broken homes (e.g., Csillag and Hedri, 1949; Tillmann and Hobbs, 1949). Biesheuvel and White (1949) in a study of accidents among South African Air Force pilots recorded that "there was a highly significant difference between the accident and control groups in respect of the numbers of cases where the father had died."

Method

The statistics were collected from Royal Air Force personnel who attended for electroencephalographic examination. The medical officers by whom the patients were referred were wholly unaware of the inquiry and therefore it cannot be argued that they tended to send especially those with a history of deprivation. Only patients aged 18–29 were questioned. The questions were read out from a standard written form and the answers recorded in code and on punched cards. The standard form of questioning was rigidly adhered to in order that it might be possible to refute any complaints that improper questions had been asked. Though details of divorces and brutality were often volunteered, they were never asked for.

The questions were, "Are both your parents alive?" If the answer was in the negative the age of the patient at the time of the death was ascertained. "Can you remember, to the best of your ability, whether at any time during your youth or childhood you were separated from one or other of your parents for a period of about six months or longer, for any reason at all—for instance, your father in the Army, you evacuated, you or your parents in hospital, or *any other reason whatever?*" Where there was a history of separation, only the first episode of six months was recorded. Thus, multiple separations over the years, or continued separation, were arbitrarily classified under the age when the first separation occurred.

In most instances these questions were put, and the information was recorded, by the electrophysiological technicians of the department. They were carefully instructed in what to do, and were reliable and intelligent—four were university-educated, two were awaiting entrance to a university, and the other three were of comparable ability. Before the statistics were recorded the patient's diagnosis was noted from the request form for an E.E.G. The diagnoses were arbitrarily grouped as E for epilepsy, P for psychiatric case, O for "other," HS for head injury (self-responsible), and H for head injury (not responsible).

It is important to note that the E group differs from those encountered in civilian hospitals. Nearly all had had only one or two fits, and the first of these had generally occurred in the Service. Chronic epileptics, whose families might have been disturbed thereby, were not encountered. A few neurotic patients who received the benefit of any doubt in the diagnosis of "black-outs" are probably included (which merely makes the observed differences from the P group more real).

The P group contained especially patients classifiable as of "inadequate personality," referred according to the varying tastes of their medical officers—especially if headaches, "dizzy spells," and aggressive behaviour were prominent.

The O cases were assorted neurological patients and cases of definite migraine, cardiovascular syncope, etc. It was expected that this group might contain a fair sprinkling of neurotics, and for this reason the hypothesis at the outset was that there would be a significant difference between the E and P groups and that the O group should be ignored.

The groups H and HS were made up of (*a*) those referred on account of head injury, and (*b*) those referred primarily for some other reason, but who, on routine pre-electroencephalography questioning, stated that within the previous two years they had had a head injury of sufficient severity to cause unconsciousness. The head injuries were also classified into groups—"driver," "passenger," "sport," and "other." These figures are not presented owing to the smallness of these groups. The decision on whether the individual was responsible or not for his injury was always made before the family history was taken; and while the P, E, or O diagnoses were occasionally altered on the basis of later information, the H or HS diagnoses were never altered. Emphasis was placed on severity in allotting responsibility, and, while passengers were mostly H cases, only two drivers were treated thus leniently.

Hypotheses at Outset

The initial hypotheses were: (1) that there would be an excess of cases of deprivation in the P group when compared with the E group; (2) that there would be an excess of cases of deprivation in the HS group when compared with the H group. As previously stated, the O group was to be ignored. The groups E and H were both expected to be normal control groups, and, as there are no cross-diagnoses between these two groups, they could be added if desired.

The distribution of the different varieties of deprivation in each diagnostic group is shown in the Table.

Frequency of Deprivation of Parents

Diagnostic Group:	P	E	O	HS	H
Total No. of cases in group	271	119	245	245	91
No history of deprivation	114	67	132	118	49
Deprivation of any kind at any age	157	52	113	127	42
" " " " " ages 0–5 inclusive	87	32	61	68	23
Deprived by death or separation for 6 months from *both* parents at ages 0–5 inclusive	36	5	18	16	2
Mother dead	20	11	11	20	8
Age at mother's death, 0–5 years	7	3	6	10	3
" " " " 6–10 "	4	4	3	3	0
" " " " 11–15 "	3	4	0	2	2
" " " " 16–20 "	6	0	2	5	3
Separated for 6 months from mother	62	9	34	31	17
Age when separated, 0–5 years	33	4	18	12	8
" " " 6–10 "	19	5	10	12	5
" " " 11–15 "	10	0	6	7	4
Father dead	42	17	32	36	10
Age at father's death, 0–5 years	17	7	12	11	5
" " " " 6–10 "	6	2	4	6	0
" " " " 11–15 "	10	2	11	9	3
" " " " 16–20 "	9	6	5	10	2
Separated for 6 months from father	110	34	81	87	27
Age when separated, 0–5 years	63	21	41	50	16
" " " 6–10 "	33	11	30	29	7
" " " 11–15 "	14	2	10	8	4

Discussion

No elaborate analysis of the figures is justified when the initial hypotheses are borne in mind. However, it may be noted that the first of these hypotheses is confirmed. If the P and E groups (there were no cross-diagnoses between these groups) are compared in respect of those with a history of deprivation of any kind and those without such a history, there is a significant difference between them ($\chi^2=6.7$, $P=0.01$). This difference could be interpreted as indicating that deprivation of parents increases liability to mental ill-health (though no figures for a probably more important history of unhappiness, brutality, etc., are available). Alternatively, it could be claimed that the mentally unstable tend to exaggerate a history of parental loss, or that they inherit their predisposition from parents whose own instability contributed to the breakdown of home life. Or, again, it is possible that the mentally healthy forget or gloss over parental deprivation. The difference between the two head injury groups is in the expected direction, but is small and not significant.

The effects of wartime evacuation of children, and war service by the father, on these statistics, which were collected during 1956 and 1957, are very obvious in the high incidence of separation from parents in the early age groups.

The Table shows also a high recorded incidence of death of fathers, and, to a less degree, mothers, for the age group 0–5 years. In this connexion it should be remembered that this group covers six years of life, unlike the other groups. Wartime casualties, particularly among the fathers, must also be considered. Even so, the incidence of maternal deaths in this period still seems high, and may be accounted for (*a*) because in the case of the P and HS groups such maternal loss does, in fact, cause behaviour disturbances, or (*b*) because of unreliability inherent in the nature of the inquiry. While it is reasonable to compare the different groups, the absolute figures may need to be treated with caution because of the rigid form of the questions asked. There was no mandate for questions about illegitimacy or adoption; and, indeed, to ask such questions of a patient referred for E.E.G. examination because he had crashed his aircraft and sustained a head injury might have led to justifiable complaints. Consequently the figures for the 0–5 age group, in particular, may be distorted owing to untrue or evasive answers.

Summary

The frequency of deprivation of parents during the childhood of a series of young Service men was investigated in relation to diagnosis. Significantly more of those who were psychiatric cases had a history of deprivation than cases referred on account of isolated epileptic attacks.

There was not a significant difference between a group of persons responsible for accidents and a control group.

The investigation was possible because of the co-operation of the electrophysiological technicians of the department. I thank Group Captain V. H. Tompkins, principal specialist in neuropsychiatry, Royal Air Force, for his encouragement. The present investigation was among those carried out during the period of tenure of a British Medical Association Research Scholarship.

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RESPIRATORY INADEQUACY AFTER THORACIC SURGERY IN TUBERCULOUS PATIENTS

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Respiratory function is always impaired to a greater or lesser degree after thoracic operations. The following factors, acting singly or in combination, are likely to reduce pulmonary ventilation: infection; paradoxical respiration, especially following thoracoplasty; lobar or lobular atelectasis; compression of the lung by air or fluid; pulmonary congestion or oedema; reduction of functioning lung tissue by disease or resection; wound pain, limiting chest expansion; and drugs, particularly analgesics and sedatives.

Most patients have a respiratory reserve sufficient to surmount these temporary difficulties, and measures such as physiotherapy, water-seal drainage, antibiotic therapy, and occasional bronchoscopy are usually adequate to prevent serious complications in the post-operative period. Many, however, whose respiratory reserve is grossly reduced by disease are now accepted for surgery. We have anaesthetized several with a pre-operative maximal voluntary ventilation (M.V.V.) of less than 30 litres a minute and in one it was as low as 17 l./min. Such patients require very careful pre-operative preparation, meticulous anaesthetic and surgical technique, and vigilant post-operative supervision.

Occasionally, despite careful post-operative management, the usual measures do not prevent the development of respiratory inadequacy, the features of which are due to hypoxia and carbon dioxide retention. When the main cause of respiratory insufficiency is atelectasis, ventilation may be sufficient to maintain the carbon dioxide tension of the blood within the normal range, but hypoxia may be severe as a result of impaired diffusion of oxygen and the shunting of blood through non-ventilated alveoli. When hypoventilation is due mainly to factors other than atelectasis, both hypoxia and carbon dioxide retention will be present. It must be noted, however, that the administration of oxygen to such patients will relieve the hypoxia and thereby remove the reflex respiratory drive from the chemoreceptors, thus aggravating the retention of carbon dioxide.

Method

When it was decided that respiratory inadequacy was present, a wide-bore cuffed tube was passed under direct-vision laryngoscopy through the mouth into the trachea. If the patient was not already deeply unconscious, light general anaesthesia was induced to facilitate intubation. A period of hyperventilation through soda-lime followed, the patient's level of consciousness being assessed from time to time. A tracheostomy was made through the second and third tracheal rings in those patients who had considerable retention of secretions and who were likely to require a respirator for more than 24 hours. A shortened endotracheal tube fitted with a Magill T piece was inserted into the trachea, the cuff inflated, and connexion made to a mechanical respirator. Secretions were aspirated at frequent

intervals through a Tiemann catheter which had been modified by shortening and smoothing the tip so that it might be passed in turn easily and atraumatically down each main bronchus. In the five cases described the "pneumomatic" respirator was used (Horton, Inkster, and Pask, 1956). An air-entraining device attached to an oxygen cylinder provided an air/oxygen mixture to operate the machine and ventilate the patient. A humidifier of the type described by Marshall and Spalding (1953) was inserted between the respirator and the patient.

Case 1

A thin, undernourished man of 43 was found in 1938 to have bilateral pulmonary tuberculosis. In 1942 a right artificial pneumothorax and phrenic crush was carried out. In March, 1956, the vital capacity was 1,810 ml., the timed vital capacity was 1,120 ml. in 2 seconds, and the M.V.V. 38 l./min.

Differential lung function tests at that time were as follows:

	Tidal Air	Vital Capacity	Oxygen Uptake
Right lung ..	15 ml.	50 ml.	19 ml./min.
Left ,, ..	250 ,,	1,450 ,,	235 ,,

In April, 1956, a right pneumonectomy was performed. The immediate post-operative condition was satisfactory, but on the following day respiration became shallow and bubbling and the patient lapsed into unconsciousness. Bronchoscopy was carried out, and had to be repeated twice in the following four hours to remove accumulated secretions. Since respiration remained inefficient and laboured, tracheostomy was performed and intermittent positive-pressure respiration (I.P.P.R.) commenced. Radiological examination on the next day showed full expansion of the left lung. The respirator was used for 10 days. At the time of writing this patient was still receiving sanatorium treatment but his condition was satisfactory.

Case 2

The patient was a woman of 52 with bilateral pulmonary tuberculosis. In December, 1956, she had a right upper thoracoplasty. Her post-operative course was rather stormy; she had some paradoxical breathing and was cyanosed without oxygen, but she recovered without artificial respiration. In March, 1957, the M.V.V. was 21 l./min. Left upper thoracoplasty was carried out in May. The immediate post-operative state was fairly satisfactory, but gradually, over the next fortnight, the patient became more and more dyspnoeic. She appeared to be exhausted and was unable to cough effectively. After 15 days she was confused, disorientated, and cyanosed without oxygen. Tracheostomy was carried out and I.P.P.R. started. The carbon-dioxide-combining power of venous blood was 98 volumes per 100 ml., and by the following morning this had increased to 106 volumes per 100 ml. Once the initial difficulties in tolerating the tracheostomy tube had been overcome the carbon-dioxide-combining power fell steadily and after five days was 75 volumes per 100 ml. The respirator was in use continuously for six days and weaning took a further three days, after which recovery was uninterrupted and the patient was discharged to a sanatorium a month later.

Case 3

A small, thin woman of 25 had been under medical treatment for bilateral pulmonary tuberculosis since 1950. In February, 1957, a right extrapleural plombage was carried out. In March her lung functional capacity was as follows:

Test	Actual Result	Predicted Result
M.V.V.	19 l./min.	90 l./min.
Vital capacity	1,100 ml.	3,100 ml.
Timed V.C.	700 ml. in 2 secs.	2,700 ml. in 2 secs.

She had no dyspnoea when at rest in bed. In April a right upper thoracoplasty was carried out under general anaesthesia and the plomb removed. The patient recovered consciousness rapidly following the operation and was returned to the ward. Within a few hours, however, the respiratory paradox increased and the level of consciousness became depressed. When the anaesthetist was recalled, a cuffed tracheal tube was passed and hyperventilation was carried out manually through a Waters canister for an hour with frequent aspiration of secretions. She recovered consciousness but tolerated the tube well. Thereafter, I.P.P.R. was continued with the pneumomatic respirator via the tracheal tube for 12 hours. A radiograph of the chest showed that the lungs were well aerated. The concentration of electrolytes and the carbon-dioxide-combining power of venous blood were within normal limits. Following withdrawal of I.P.P.R. spontaneous respiration rapidly became adequate, and thereafter her convalescence was uneventful.

Cases 4 and 5

These two cases have been reported more fully by Robson (1958).

Case 4.—A woman of 46 had twenty years' history of pulmonary tuberculosis. Seventeen years previously, she had had a right upper seven-rib thoracoplasty, which, however, had not closed the cavity. The disease was unilateral and tubercle bacilli were present in the sputum. A right pneumonectomy was carried out under general anaesthesia. Nine days after operation she developed an infection in the other lung, and respiratory efficiency was further impaired by continuing paradoxical respiration. On the twelfth day after operation she was cyanosed and unconscious. At this time the oxygen saturation of the arterial blood was 65%, the arterial carbon dioxide content 97 vols. per 100 ml., and the *p*H 7.3. After she had been intubated and hyperventilated with oxygen, a tracheostomy was made and respiration taken over by the pneumomatic respirator. Subsequent gas analysis of the arterial blood showed a steady decline in carbon dioxide content with a rise in oxygen saturation to normal levels. Artificial respiration was continued for three weeks, by which time the right thoracic cage had healed firmly and there was no paradox when the patient breathed spontaneously.

Case 5.—A right upper four-rib thoracoplasty was performed under general anaesthesia on an emaciated, ill-looking man of 58. Two months previously a right upper lobectomy and apical lower segmental resection had been carried out. On the fourth day after the thoracoplasty an obvious bronchopleural fistula developed from an empyema cavity which communicated with the subscapular space. The patient was cyanosed and dyspnoeic. He was intubated and ventilated manually until his condition improved. Then a tracheostomy was made and I.P.P.R. by respirator initiated and continued for 24 days. Fourteen days after I.P.P.R. was discontinued the patient died of coronary thrombosis. At necropsy there was, in addition, a small area of necrosis on the posterior wall of the trachea. This was almost certainly due to pressure by the tip of the inadequately curved tube.

Discussion

Björk and Engström (1955) described the treatment of 15 patients with respiratory insufficiency following pulmonary resection by tracheostomy and prolonged artificial ventilation. Their patients were classified in two groups: (1) those who developed infection in the only functioning lung, and (2) those who already had a "compensated ventilatory insufficiency" before operation.

We have already mentioned the factors which may, singly or collectively, cause post-operative respiratory inadequacy. In our experience, respiratory paradox and infection have been the most important in those cases requiring treatment by I.P.P.R., which is, of course, only a temporary expedient

to maintain pulmonary ventilation until these complications can be controlled. During the actual operation paradox is prevented by controlled ventilation. However, it may occur when spontaneous respiration is resumed after operation. This risk remains so long as the chest wall is mobile, which may be a matter of weeks. Most patients compensate for this by an increase in tidal volume. But when the vital capacity is little more than the tidal volume there is no possibility of effecting much increase, and a small degree of paradox may precipitate ventilatory insufficiency (Case 2). Equally, respiratory paradox, when associated with some other pulmonary complication—for example, infection—may make it necessary to assist respiration (Case 4). In four of the five patients described above, paradox was an important factor. In three of them artificial respiration was continued until the chest wall was firmly healed.

The pneumomatic respirator has proved efficient and reliable. Various minor technical difficulties in the working of the machine over long periods have been encountered, but these have been reduced to a minimum by regular maintenance. An oxygen cylinder and a Waters canister containing soda-lime are kept constantly available at the bedside lest difficulty with the machine should develop. The nursing staff in attendance are instructed in the technique of manual ventilation so that they can, should the need arise, keep the patient alive until medical help arrives.

In the day-to-day management of these patients clinical appraisal is most important. Sweating and a rise in blood pressure usually signify carbon dioxide retention. Frequent clinical and radiological examination is necessary to ascertain that air entry into the chest is adequate. Air flow may be interrupted partly or completely by such factors as secretions, kinked tubing, prolapse of the cuff, or an excessively long tracheostomy tube. Obstruction from this latter cause is most likely to occur if the tracheostomy has been made too low. A pressure-cycled machine will continue to operate even if the airway is completely obstructed, since it is triggered by pressure of gas within the machine. In these circumstances the rate will increase, since the "blow off" pressure is reached more quickly. Nurses are taught to observe the patient's colour and the rise and fall of the chest, and to report any increase in the rate of operation of the machine. Pulmonary secretions are tested for antibiotic sensitivity and the appropriate drug is given.

Most of our patients have had a low-grade pyrexia which cleared up rapidly after the tracheostomy tube was removed. Water must be drained from the expiratory side of the circuit and the temperature of the humidifier checked at regular intervals. The patient's position is changed every few hours to prevent hypostatic congestion, to encourage postural drainage of secretions, and to avoid bedsores. Pressure on the trachea by the endotracheal tube and cuff has, however, been a problem (Case 5). In an attempt to minimize this danger the cuff is deflated for a few minutes every two hours. The length of time that it can remain deflated is limited, since cycling is prevented by the escape of gas round the tube and the machine is brought to a standstill. Damage due to movement or pressure of the shortened endotracheal tube should be reduced to a minimum by a moulded rubber tube of the type described by Spalding and Smith (1956). Since pooling of pharyngeal secretions may occur above the cuff, pharyngeal toilet is carried out immediately before it is deflated, and suction through the tube is practised while it is collapsed. The tracheostomy tube is left until a firm track has formed, usually in four or five days. Thereafter it is changed every two days or oftener if there is any danger of the tube becoming blocked by secretions. The tracheal stoma is cleaned with ribbon gauze; cotton-wool should not be used as fragments may be left in the trachea.

The importance of having well-trained and alert nurses cannot be too strongly emphasized. Patients on I.P.P.R. become very dependent on the machine and on their usual medical and nursing staff. A new nurse must not be left in sole charge until she is thoroughly capable of dealing with any emergency which may develop and, if the patient is conscious, until she has fully gained his confidence. Respirator patients quickly detect any lack of experience or knowledge on the part of their attendants and may become apprehensive. The confidence of the patient is particularly required during weaning from the machine. At this stage a patient-triggered respirator is a great advantage. Short spells of spontaneous respiration are gradually lengthened until I.P.P.R. is no longer necessary.

These patients are in some respects difficult to manage. Functioning lung tissue is reduced, sometimes markedly, so that it may be difficult to hyperventilate the patient and correct an existing respiratory acidosis. Lung compliance is often reduced, and a higher pressure of gas than usual may be required to expand the lungs. Infected secretions from the tracheo-bronchial tree or from the tuberculous cavity may necessitate very frequent aspiration. If the trachea is irritable, spasms of ineffective coughing may be provoked, distressing the patient and hindering the proper working of the machine. Generally, however, the tube is well tolerated, though sedation may be required for the first day or two.

On the other hand, since the patient is not paralysed, general nursing is easier. Physiotherapy is facilitated, since active movements are possible. Although an intragastric tube is employed for feeding in the first few days, the patient is soon able to feed himself. He is better able to communicate his needs and worries to the nursing staff and is also able to read or interest himself in other ways, which is a considerable help to his morale.

Summary

Various factors which adversely affect respiratory efficiency after thoracic operations are reviewed.

A method of treatment of respiratory inadequacy by tracheostomy and intermittent positive-pressure respiration is described and illustrated by five case reports.

The important role of respiratory paradox in precipitating respiratory inadequacy is emphasized and some practical points in management are discussed.

In the efficient management of patients with respiratory inadequacy team-work is of the utmost importance. It is therefore a pleasure to acknowledge the valuable help and co-operation which we have received from our medical and surgical colleagues both in the treatment of these cases and in the preparation of this paper.

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Mr. RICHARD THOMPSON, Parliamentary Secretary to the Ministry of Health, speaking at a meeting of the Association of Hospital Management Committees at Southport on June 12, drew attention to four "deeply significant" features in the history of the past 10 years of the hospital service. First was the better use of beds. The rise in available "staffed" beds between 1949 and 1957 had been 6%, but the number of in-patients treated in them had risen by 30% during the same period. Secondly, the growing importance of out-patients departments. The number of out-patients seen at consultative clinics had increased by more than 12%, from 6,148,000 in 1949 to 6,907,000 in 1957. Thirdly, the comfort and convenience of out-patients had been studied, and attention devoted to the reduction of waiting time. Lastly, there had been a striking change in the outlook towards mental health, both on the part of the public and the hospitals. More patients were coming forward for treatment voluntarily and at an early stage. The proportion of voluntary admissions had risen from 59% in 1949 to 78% in 1957.

DISTRIBUTION OF SKIN TUMOURS OF SOLE OF FOOT

BY

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This study of skin tumours of the foot, especially those of the sole, was undertaken to find out whether pressure contributed to the dissemination of the malignant melanoma. Some unexpected clinical and anatomical facts emerged as the data accumulated, and the fundamental question itself was shown to be wrong because the melanomas in fact were not situated mainly on the weight-bearing areas of the sole.

Present Investigation

The cases of the survey consisted of 511 lesions of the foot seen in the Christie Hospital from 1932 to 1955. Many had been recorded on diagrams or photographs. Tables I and II indicate the types of cases seen and their numbers.

TABLE I.—*New Skin Lesions (Malignant). Referred 1932–55 Inclusive. Population Catchment 4.5 Million*

	Squamous-cell Carcinoma	Squamous-cell on Lupus	Basal-cell Carcinoma	Malignant Melanoma
All sites	4,823	218	11,087	478
Lesions of foot:				
Sole	31	1	—	32
Dorsum ..	21	—	—	20
Other parts or not stated ..	16	—	—	15
	68 (1·4%)	1	—	67 (14%)

TABLE II.—*New Skin Lesions (Benign). Referred 1932–55 Inclusive. Population Catchment 4.5 Million*

	Angioma	Skin Warts	Keloid	Benign Melanoma	Other Benign Conditions
All sites ..	3,645	2,801	576	347	2,289
Lesions of foot:					
Sole	6	141	—	2	20
Dorsum ..	4	12	4	2	4
Other parts or not stated	36	69	11	3	61
	46	222	15	7	85

Cases without adequate clinical records were discarded and some were reclassified histologically. All the available histological specimens were re-examined; they were mainly those of the squamous-cell carcinomas and melanomas. Microscopical appearances are not presented in this paper. It may be noted, however, that no basal-cell tumour was found.

The lesions fell mainly into five main categories: (1) squamous-cell carcinoma (Table III); (2) melanomas (Table IV); (3) malignant change occurring upon pre-existing conditions, such as burns, irradiated psoriasis, tabes dorsalis; (4) plantar warts and hyperkeratotic lesions (Table V); and (5) angiomas.

When the site diagrams were superimposed as single diagrams an unexpected and striking distribution on the sole emerged (Figs. 1–5). The melanomas almost all fell in the arch region in contrast to the squamous-cell carcinomas and hyperkeratotic lesions, which were on the metatarsal and heel sites. Subsequently, three melanomas were discovered in the arch site by routine appraisal of the feet at post-mortem examinations. The tumours arising in areas of pre-existing disease were scattered indiscriminately. Unlike all the other lesions, the angiomas could mould themselves

TABLE III.—*Squamous-cell Carcinoma of Foot (Excluding Induced Tumours)*

Sex	Registrations 1932–55	No. for Survey	Site		Age Range
			Dorsum	Sole	
Male	24	17	3	14	42–81
Female ..	10	5	1	4	57–78
Total ..	34	22	4	18	42–81

TABLE IV.—*Melanoma of Foot*

Sex	Registrations 1932–55	No. for Survey	Site		Age Range
			Dorsum	Sole	
Male	25	17	3	14	26–74
Female ..	38	25	11	14	17–81
Total ..	63	42	14	28	17–81

TABLE V.—*Plantar Warts and Hyperkeratotic Lesions*

Age Group	Male	Female
0– 9 years ..	5	9
10–19 ,, ..	16	30
20–29 ,, ..	46	20
30–39 ,, ..	25	8
40–49 ,, ..	7	4
50–59 ,, ..	7	6
60–	5	4
	111	81

The weighting between 10 and 39 years is due to Army personnel and schoolchildren seen from 1939 to 1945.

over wide surfaces extending frequently from the dorsum to the sole, or vice versa. This plasticity can be explained by the vascular nature of the lesion, and is a feature of the angioma that might be more emphasized in its clinical diagnosis.

Certain trends in age and sex distribution were also apparent. The squamous-cell carcinomas occurred more often in the male, as in other sites of origin; the melanomas seemed to be more prevalent in women. The incidence of angiomas was greater in female infants in the first year of life. The age range of patients was wider in the melanoma group than in the squamous-cell carcinoma group, and was not so heavily weighted towards the older end (Table VI).

TABLE VI.—*Age Frequency Distribution*

Age Group	Squamous-cell Carcinoma	Melanoma
0–24 years ..	0	2·3%
25–34 ,, ..	0	9·3%
35–44 ,, ..	4%	7·0%
45–54 ,, ..	12%	20·9%
55–64 ,, ..	28%	27·9%
65–74 ,, ..	28%	25·6%
75 and over ..	28%	7·0%
	100%	100%

Discussion

The outstanding feature of this study has been the graphic one of apparent sites of election for carcinomas and melanomas. A symmetrical pattern appears to be emerging on the soles of the feet regarding the development of benign and malignant melanomas. The original problem posed was the part pressure might play in dissemination of the malignant melanoma. The population surveyed was a white one wearing shoes, the weight of the body being normally carried on the heads of the metatarsals and the heels. It is here that the miscellaneous group of hyperkeratotic lesions and squamous-cell carcinomas occur. At this stage it would be fitting to quote Nicholson (1950). Boycott (1929) observed that the difficulty in most scientific work lies in framing the questions rather than in finding the answers. By the time we are in a position to know what the crucial question really is, we have generally pretty well got the answer. Nicholson comments: "We shall never frame it

if we continue in the vain hope to 'explain the cause of cancer.' How can we expect to explain before we learn, know, and understand? In the sure and certain faith that extrinsic stimuli and intrinsic reactions of the organisms together determine tumour formation, and bearing the necessary action of the former carefully in mind, the first question to be asked of biology is this: What is the mechanism of determination of the reactions of the organism?"

FIG. 1.—Squamous-cell carcinoma. Age range 42-81 years.

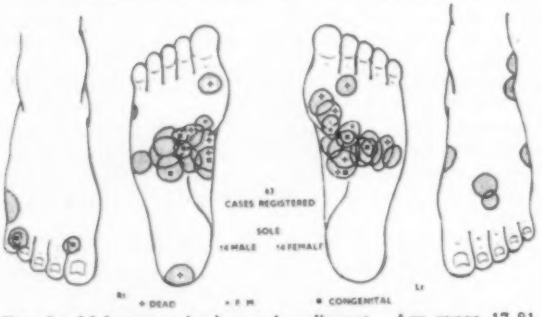

FIG. 2.—Melanomas, benign and malinant. Age range 17-81 years.

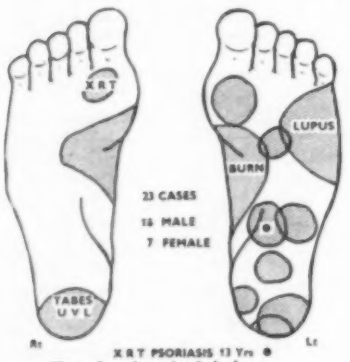

FIG. 3.—Acquired lesions.

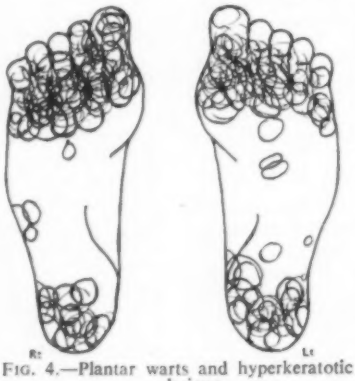

FIG. 4.—Plantar warts and hyperkeratotic lesions.

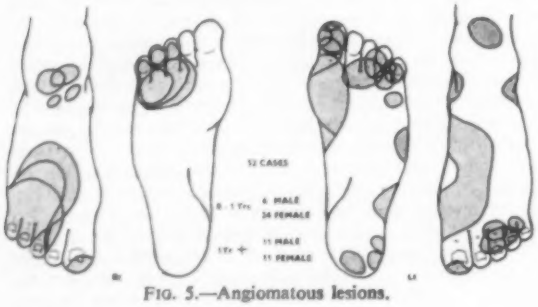

FIG. 5.—Angiomatous lesions.

The observations that the melanomas tend to occur in the arch site, where there is little weight-bearing, suggest that much more will have to be learnt before accepting pressure or irritation as the mechanism of spread, at least in the early stages.

To the best of our knowledge none of the benign hyperkeratotic lesions and warts have become malignant. The incidence of carcinoma of the foot of 1.4% is comparable to the figure Harnett (1952) quotes in the B.E.C.C. survey of 1952—1.9% of all squamous-cell carcinomas. This low incidence, when coupled with a much greater incidence of squamous-cell carcinoma in men in later years of life, suggests that the constant trauma of walking may not by itself be a prime factor in carcinogenesis.

No basal-cell tumours were seen at this hospital either on the sole or on the dorsum of the foot. Their absence from the sole agrees with the findings of Lever (1948), who has never seen such tumours on the palms of the hands or on the soles of the feet. He believes that these tumours can originate only from the so-called primary epithelial germ cell, from which hair follicles and sebaceous glands develop. These structures are not found in the palms or soles. This explanation would be acceptable, but Pascher and Sims (1954) have reported two histologically proved basal-cell epitheliomas of the sole. They revert to the hypothesis that these tumours develop from the basal-cell layer of the epidermis. The induction of such tumours has frequently been associated with prolonged exposure to sunshine. Is the absence of this or some other unknown exogenous factor another reason for their absence? Similarly, might not the induction of squamous-cell carcinomas be dependent on some factor, like the tar of the road surface, acting on the susceptible individual, as is probably the case with arsenic-induced cancers of the palms and soles?

Many of the haemangiomas of infants have a characteristic natural history, with a period of rapid growth followed by regression and subsequent disappearance. Lampe and Latourette (1957) believe that the growing phase of the lesion does not extend beyond the age of 1 year and often ceases much earlier. In their series of 346 cases the incidence of female to male infants was about 2.5:1. The effect of pregnancy on melanomas or on the growth of angiomas can be very grave, and has been attributed to increased secretion of oestrogens. It is tempting to ascribe this sex difference in the incidence of angiomas to a similar hormonal process.

Summary

The suggestion that pressure might influence the spread of malignant melanoma has led to a study of tumours of the skin of the foot. This has revealed unexpected patterns of distribution and differences in age and sex incidence without answering the original problem. These findings may be of value in diagnosis.

My thanks are due to Dr. H. Russell for her constant advice and criticism. I am indebted to the many members of the clinical staff of the Christie Hospital who have contributed to the clinical and histological data, and in particular to Miss M. H. Russell and her staff for statistical work.

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RECOVERY FROM NEUROLOGICAL SEQUELAE AFTER CARDIAC ARREST

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Cardiac arrest is a known hazard of surgical operations. Its incidence is difficult to ascertain, since not all the deaths are recognized as due to it. From recent reviews cardiac arrest would seem to occur in between 1:1,000 and 1:5,000 anaesthetics (Milstein, 1956), and in spite of greater recognition its mortality remains high.

The early recognition of cardiac arrest is all-important, for unless the heart can be restarted within three to four minutes irreversible neurological damage may occur (Primrose, 1935; Dark *et al.*, 1952; Leeds, 1953; Louttit, 1954; Milstein, 1956).

The case described below illustrates the remarkable degree of recovery which can take place following such a complication. It also underlines the importance of early recognition of cardiac arrest. The heart was restarted one and a half minutes after the condition was recognized, but the neurological sequelae suggest that the vital time interval may have been longer. In particular, since the arrest occurred just after the injection of neostigmine, the case emphasizes that this procedure should be followed by the utmost vigilance lest cardiac arrest should develop.

Case History

A 39-year-old man was admitted to hospital with a diagnosis of perforated duodenal ulcer of three hours' duration. He gave a long history of previous dyspepsia, was already known to have a duodenal ulcer, and had refused gastrectomy. The perforation was complicated by a moderate haematemesis.

At operation he was found to have a chronic duodenal ulcer on the posterior wall of the first part of the duodenum which had perforated at its postero-superior margin. The only other abnormality noticed was a large smooth fatty liver, enlarged about three fingerbreadths below the costal margin. This was associated with a history of alcoholism. Closure of the perforation proved difficult, and, in view of this, the long ulcer history, and the accompanying haematemesis, it was decided to proceed with partial gastrectomy. This was carried out without difficulty and the abdomen closed, the total operating time being 80 minutes.

Throughout the operation there was no sign of cyanosis, and while closing the wound a bleeding-point requiring ligation produced bright red blood. At the time of suturing the anterior sheath of the rectus muscle atropine, 1/100 gr. (0.65 mg.), was injected intravenously via the blood drip. Following this injection and after the pulse rate had risen to over 100 a minute, neostigmine, 2.5 mg., was injected via the drip. About two minutes later, immediately after final suture of the skin, the anaesthetist reported that the patient's pulse was imperceptible. Oxygenation produced no improvement, and five seconds later the dressing was removed from the abdominal wound and the abdomen rapidly re-entered through the previous incision.

The heart beat could not be detected through the diaphragm, and cardiac massage was immediately begun from the abdomen, the heart being compressed against the sternum. Since the heart beat did not return, 5 ml. of adrenaline 1/1,000 was injected direct into the heart through the fifth left intercostal space some 10 to 15 seconds later, and cardiac massage continued. The heart restarted immediately after the intracardiac injection of adrenaline. Heart beats were initially irregular, but within a second or two powerful regular contractions could be palpated through the diaphragm and the patient recommenced breathing. His general condition appeared excellent, and since approximately only one and a half minutes had elapsed from the time of the initial alarm the prognosis was thought to be good. The abdominal wound was again resutured and the patient returned to the ward.

Six hours later he had not recovered from the anaesthetic; strong pressure over the eyeballs failed to elicit any response, and a state of decerebrate rigidity was present, all four limbs being spastic. Superficial and deep reflexes were absent.

About eight hours after completion of the operation his temperature was 103° F. (39.4° C.), and it was decided to institute cooling. This was accomplished by ice-packs and fans, associated with chlorpromazine hydrochloride medication. The temperature fell to 99° F. (37.2° C.) during the next two to three hours and was maintained at that level by cooling for the next 48 hours.

During the first 24 hours the depth of unconsciousness remained unchanged, all four limbs remaining spastic.

On the second post-operative day the patient was still unconscious, but could be roused by non-painful stimuli, such as shouting. He became very restless and the spasticity in all four limbs had lessened He was able to swallow water and made incoherent mumbling noises. His temperature had reached the normal range and cooling was discontinued.

By the following day he had become completely conscious and would turn his head towards any sound or voices. He was totally blind, but could speak, though the words were barely recognizable because of extreme dysarthria. Leg-muscle tonus had returned to normal, but both feet gave an extensor response to the Babinski reflex. His arms remained moderately spastic and he had no control of the small muscles of the hand.

During the ensuing week arm spasticity passed off and in the next two months his muscle power returned to normal and no definite abnormality could be found in his motor system. He was able to walk about and to dress and feed himself. At this time peripheral vision had improved, the right eye being 6/36 partly, and left eye 6/24 partly. There was still considerable loss of vision; the pupils were equal and reacted to light, both directly and consensually. Ocular movements appeared to be full in all directions. There was no diplopia or nystagmus. Optokinetic nystagmus was easily elicited, both horizontally and vertically. The right optic disk was pale, particularly in its temporal half; the left optic disk appeared normal, and visual fields showed scotomata. Three months later the optic disks were considered to be normal on ophthalmoscopic examination. Vision in the right eye was 6/36 partly and that of the left 6/24 partly. A distinct reduction in the extent of the central part of the scotomata accompanied a marked subjective improvement in vision.

The patient was able to talk intelligently and no psychosomatic abnormality could be noticed. Apart from his impaired vision he appeared normal in all other respects.

Discussion

This case illustrates the remarkable recovery which may follow neurological damage occurring during cardiac arrest. It indicates that even a state of deep unconsciousness should not be regarded as completely hopeless, and probably the

use of hypothermia is justified in these cases, since it may reduce the metabolic needs of damaged nervous tissue.

As has been recorded, cardiac arrest developed in this patient within two minutes of the injection of neostigmine. The neostigmine had been given following intravenous atropine. In recent years some controversy has developed regarding which of these two drugs is the more responsible for cardiac arrest. Bain and Broadbent (1949) thought atropine partly responsible. They noted that subcutaneous injections of atropine first slowed the heart rate, tachycardia occurring only 15 to 20 minutes later. Pooler (1957) also blamed atropine. It has been shown by Johnstone (1951) that hyperventilation with CO_2 produced electrocardiographic irregularities, and Pooler noticed that intravenous atropine during CO_2 retention produced a wildly irregular pulse.

In our patient intravenous atropine produced no detectable irregularity of the pulse: tachycardia was produced, not bradycardia, and intravenous atropine produced no detectable irregularities of the pulse when given during anaesthesia after muscle relaxants in over 40 other patients.

These observations suggest to us that neostigmine was the most likely cause of cardiac arrest in the present case. This finding is in keeping with the views of many other workers as recorded by Pooler (1957). It emphasizes the need for the utmost vigilance immediately after the administration of neostigmine. The neurological sequelae in this case suggest that some valuable time may have been lost before the alarm was given.

Unfortunately, neostigmine is administered at the end of the operation, when an anaesthetist is often forced to busy himself with the many tasks involved in terminating one anaesthetic and preparing for the next. Some visual or audible method of monitoring the patient's pulse might be of great service both in the operating theatre and in the recovery-room, saving valuable seconds between the cessation of the pulse and the application of adequate cardiac massage.

Only by such methods can delay in recognition be prevented, and this factor may well contribute to the continuing high mortality of cardiac arrest in spite of more adequate surgical management.

Summary

A case of recovery from neurological damage following cardiac arrest is described.

Neostigmine was given two minutes before arrest of the heart, and was thought in this case to be the most responsible agent.

The need for some mechanical device to monitor the pulse during operation is emphasized, so that treatment could be initiated in the shortest possible time following stoppage of the heart.

We thank Professor C. F. W. Illingworth, in whose wards this patient was treated, for guidance in the preparation of this paper, and Dr. M. W. Paterson, of the eye department, Western Infirmary, for superintending the ophthalmological investigations carried out on this patient.

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The *Transactions and Report* of the Liverpool Medical Institution for the year 1957 contains the inaugural address by Dr. MARGARET E. THOMAS, the first lady president of the Institution, who took for her subject "The Artist's Contribution to Medicine." Also included are abstracts of papers read at ordinary meetings.

HAEMORRHAGE DURING PHENINDIONE THERAPY

BY

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Anticoagulants have an accepted place in the immediate treatment of thrombotic diseases. Their value in the prophylaxis of thrombosis has yet to be established. The risk of haemorrhage, and possibly death as a consequence, is a hazard to which increasing numbers of patients are exposed as the use of these drugs and the duration of treatment extend.

Reports of the incidence of haemorrhage attributed to anticoagulant therapy relate mainly to the more extensively used coumarin group of drugs. The frequency of this complication has varied, but it would appear that experience has not succeeded in reducing the risk of haemorrhage during long-term anticoagulant therapy. The incidence of haemorrhage in patients treated with anticoagulants over a period of five years was 36% in Nichol and Borg's (1950) series and 42% in the series of Keyes *et al.* (1956); Peyman (1957), over a period of one year, found a haemorrhagic incidence of 23%. Similarly with short-term anticoagulant therapy, the frequency of haemorrhage has not decreased: Olwin (1949) reported an incidence of 15%, Gilchrist and Tulloch (1954) 11%, and Peyman (1957) 16%.

It is possible that significant haemorrhage during anticoagulant therapy may be forecast by using a simple chemical tests ("occultest") to detect microscopic haematuria (Peyman, 1956). Should significant bleeding occur with anticoagulant therapy, it is essential that adequate means should be available to overcome this complication. Toohey (1953) has discussed the indications for oral and intravenous vitamin K_1 in combating haemorrhage induced by anticoagulants. This paper is concerned with the treatment of haemorrhage and factors which may have influenced the onset of bleeding in a series of patients receiving phenindione ("dindevan").

Method

Patients were treated with twice-daily doses of phenindione, and prothrombin estimations were done each day by Quick's one-stage method, using brain extract as a source of thromboplastin. Phenindione dosage was assessed from the previous response of the patient to the drug, so that the prothrombin time was kept within the desired therapeutic range between two and three times the control prothrombin time. The duration of phenindione treatment varied between individual patients from 3 to 12 weeks, the majority receiving this therapy for a period of three to four weeks. A total of 92 patients were treated with phenindione: myocardial infarction 69, venous thrombosis 3, pulmonary embolism 15, others 5. Six deaths occurred during the period of observation; in one case death was attributed to phenindione. Four died in left ventricular failure and one from mesenteric embolus one week after stopping phenindione.

Major haemorrhage occurred in seven patients (7.6%) (see Table), one of whom died as a direct result of this complication. Minor haemorrhage—for example, microscopic haematuria (Peyman, 1956)—was not sought.

Treatment of Haemorrhage

The immediate danger of haemorrhage is determined by the presence of shock. This will occur with a sudden large haemorrhage. In a patient who is receiving anticoagulant therapy for a myocardial infarction the adverse circulatory effects associated with shock will cause further myocardial damage. Fatalities may be avoided if shock can be overcome before irreversible changes occur in the myocardium. Early blood transfusion is of paramount importance in this respect. Transfusion will correct the circulatory defects and prevent further myocardial damage, and, by increasing the prothrombin concentration, will diminish the likelihood of further haemorrhage.

By anticipating sudden massive haemorrhage, arrangements can be made for immediate blood transfusion. Specific inquiry should be made in all cases subjected to anticoagulant therapy regarding a past history of dyspepsia or of known peptic ulceration, since bleeding from this source is likely to be sudden and severe. It would be prudent to retain a blood sample from these patients on admission, so that, should haematemesis or melaena occur, blood can be cross-matched and transfused at the earliest opportunity. The value of early blood transfusion for massive haemorrhage is well illustrated in this series. In Case 4 an 84-year-old woman was severely shocked by the sudden gastric haemorrhage but made a striking clinical improvement after early blood transfusion. Melaena occurring in Case 6 was not associated with shock. Although phenindione therapy was stopped and intravenous vitamin K_1 given, a further haemorrhage occurred the following day. On this occasion the patient was shocked, and he died within 30 minutes. When melaena subsequently occurred in Case 7, earlier experience dictated immediate blood transfusion and the patient made a good recovery.

Death is uncommon when haemorrhage, although severe—for example, profuse haematuria—is unassociated with shock. Sudden loss of a large volume of blood into the renal tubules is unlikely, and even gross haematuria usually subsides within 48 to 72 hours of stopping anticoagulant therapy. Haematuria ceased in Cases 1 and 2 when phenindione therapy was stopped; no further measures were required. In Case 3 profuse haematuria continued unabated for three days, and it was thought advisable to give oral vitamin K_1. The quantity of blood in the urine rapidly diminished and within 24 hours macroscopic haematuria had disappeared. Severe loin pain coinciding with the onset of haematuria and continuing was considered to be an indication for intravenous vitamin K_1 in Case 5. The loin pain persisted for a further 12 hours before subsiding; haematuria gradually decreased, and by the fourth day there was no macroscopic evidence of bleeding.

Factors Influencing the Onset of Haemorrhage

Although a pre-existing lesion determined the site of haemorrhage in six of the seven patients who bled, a potentially haemorrhagic lesion was present in 38% of the patients who did not bleed. The frequency of haematuria and gastro-intestinal bleeding in this series was, however, far greater than similar haemorrhage in patients with known lesions of the genito-urinary tract or peptic ulceration receiving other forms of hospital treatment. It is therefore unlikely that fortuitous rupture of damaged vessels was the cause of bleeding with phenindione therapy.

Five of the seven patients who bled received a daily average dosage of phenindione much higher than that required by the non-bleeders in this series. The patient who received the highest average dosage (Case 5) was the only one without a pre-existing lesion. There were, however, individual patients amongst the non-bleeders who tolerated phenindione in amounts as high as those who subsequently bled, though none so much as Case 5. Neither age nor estimated "prothrombin" activity was related to the onset of haemorrhage.

It must be concluded that localized vascular damage will not alone cause haemorrhage during phenindione therapy; by forming the weakest links in the vascular chain it could determine the *site* of haemorrhage. Excessive administration of phenindione might precipitate bleeding.

Summary

In a series of 92 patients treated with phenindione, major haemorrhage occurred in seven, one of whom died.

Early blood transfusion is of paramount importance when a sudden large haemorrhage occurs during phenindione therapy.

Factors which may have induced bleeding are discussed.

I thank Dr. M. M. Deane, Dr. P. M. McAllen, Dr. K. Shirley Smith, and Dr. N. S. Plummer for permission to use their patients from the West Middlesex and Charing Cross Hospitals.

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Case Histories of Patients who Bled During Phenindione Therapy

Case	Sex	Age	Diagnosis	Pre-existing Lesion	Site of Haemorrhage	Treatment	Course	Result	Average Daily Phenindione
1	M	55	Myocardial infarction	Urinary infection 12th day	Haematuria 19th day	Anticoagulants stopped	Bleeding ceased after 3 days	Discharged to convalescence	175 mg.
2	M	43	Syndrome of impending cardiac infarction	Renal calculus 15 years previously	Haematuria 26th day	,,	Bleeding ceased in 24 hours	,, ,,	160 ,,
3	M	49	Myocardial infarction	Urinary infection 10th day	Haematuria 21st day	Anticoagulants stopped. Oral vit. K_1 3rd day	Bleeding ceased after 4 days	,, ,,	165 ,,
4	F	84	,, ,,	30 years' history of dyspepsia. Proved G.U.	Haematemesis 18th day	Anticoagulants stopped. Blood transfusion within 1 hour of haemorrhage	No further bleeding	,, ,,	100 ,,
5	M	62	,, ,,	—	Haematuria 17th day	Anticoagulants stopped. Vit. K_1 I.V. 2nd day	Bleeding ceased after 4 days	,, ,,	260 ,,
6	M	62	,, ,,	Dyspepsia for many years. Chronic D.U.	Melaena 12th day. Further profuse melaena 13th day; associated shock	Anticoagulants stopped. Vit. K_1 I.V. at time of initial haemorrhage	Died 30 minutes after recurrence of bleeding	Necropsy: Myocardial infarction. Ruptured atheromatous artery in base of chronic D.U.	160 ,,
7	M	65	,, ,,	Recurrent dyspepsia for many years. D.U.	Melaena 26th day; associated shock	Anticoagulants stopped. Immediate blood transfusion	No further bleeding	Discharged to convalescence. A subsequent barium-meal examination showed a deformed D.U. cap	100 ,,

Medical Memorandum

Remote Prognosis in Tuberculous Peritonitis

When extensive calcification is found in soft tissues there is a tendency to regard this as a permanent change. The following case is therefore of interest.

CASE REPORT

A male child had been in good health until the age of 19 months, when he developed bronchopneumonia, after which he had failed to pick up. There had been loss of appetite and weight, vomiting, abdominal distension, and severe constipation. Admission to hospital at this time had revealed the presence of ascites. His Mantoux reaction was positive and he was treated with streptomycin for three months. On discharge his constipation had improved, his vomiting had ceased, but in other respects his general condition remained much the same as on admission. Excessive thirst and polyuria were noted at this time.

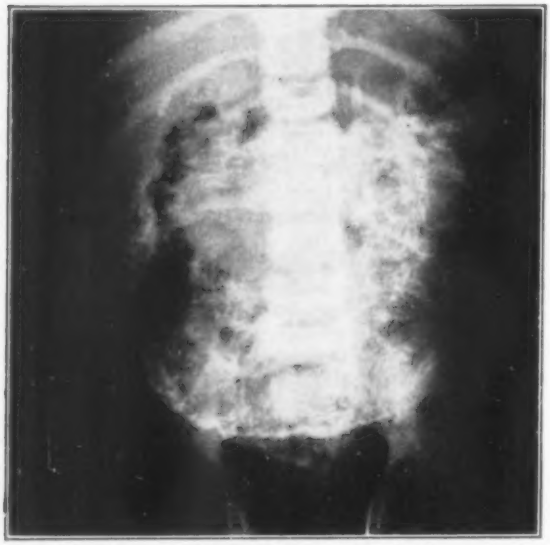

FIG. 1.—Radiograph taken in June, 1950, showing numerous calcified masses.

FIG. 2.—Radiograph taken in October, 1956, showing great reduction in size of calcified masses.

He was admitted to the Royal Manchester Children's Hospital at the age of 2 years 2 months with anorexia and constipation. He weighed 22½ lb. (10.2 kg.), and presented with an asymmetrically distended abdomen, "ladder-patterning" of the gut in the epigastrium, and several large firm masses in the right flank and right hypochondrium. His temperature was normal, the E.S.R. 38 mm., and chest *x*-ray picture normal. An abdominal *x*-ray film showed numerous calcified masses (Fig. 1). Bowel actions were infrequent and he required enemata from time to time. His fluid intake varied from 20 to 40 fl. oz. (0.6 to 1.2 l.) a day. During the four months prior to admission he had been receiving syrup "minadex," 3 fl. dr. (10.6 ml.) daily and "glucodin," 1 lb. (0.5 kg.) a week, giving a total daily intake of 1,600 I.U. of vitamin D from these sources. Serum calcium was 14.8 mg./100 ml., phosphorus 4.7 mg./100 ml., and blood urea 72 mg./100 ml. There was a moderate albuminuria. Despite these findings, operation was decided upon because of the suspicion that there might be calcification in a neuroblastoma, and the clinical picture was consistent with that view.

At laparotomy the peritoneal cavity was characteristic of healed plastic tuberculous peritonitis—that is, fibrous thickening, masses of calcified material, and matting together of coils of small intestine, some of which were distended. A peritoneal biopsy was carried out to confirm the diagnosis. The prognosis was thought to be poor, because intestinal obstruction seemed almost inevitable sooner or later. A five-months course of streptomycin was given, to which *para*-aminosalicylic acid was added later. The blood urea fell slowly, but after three months the serum calcium was still high (13.3 mg./100 ml.). The E.S.R. became normal after five months. After seven months in hospital the child was discharged, having gained 4½ lb. (2 kg.) in weight, with regular bowel actions, and somewhat improved in general condition. The abdominal distension was unchanged.

By October, 1956, six years later, the improvement was most striking and unexpected. He was of normal height and weight for his age, the abdomen was of normal contour, and no masses were palpable. Radiologically the calcified masses were greatly reduced (Fig. 2). He was entirely free from symptoms.

COMMENT

The prognosis of tuberculous peritonitis has been greatly improved since the introduction of streptomycin (Ravina *et al.*, 1948; Grant *et al.*, 1951; Salmon, 1951), and the disappearance of ascitic fluid on treatment is usually rapid (Diwany and Gabr, 1952). Striking resolution of intra-abdominal masses may occur (Barron, 1948; Wichelhausen and Brown, 1950; Diwany and Gabr, 1952), but I have been unable to find a comparable case report where large calcified masses have practically disappeared. The introduction of isoniazid has led to much further improvement in results of treatment, but this drug was not available at the time. It is interesting to speculate on the possibility that similar resolution might occur in calcified tissues in other situations—for example, in the pleura, lung, subcutaneous tissues, kidney, and muscle—once the causative factors have ceased to operate.

I thank Professor Wilfrid Gaisford for permission to report this case and for kindly reading the text. My thanks are also due to the department of clinical photography, Manchester and Salford Hospital for Skin Diseases, for the photographs.

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Reviews

WORLD MEDICAL ASSOCIATION

First Decade Report of the World Medical Association, 1947–1957. ($2.) World Medical Association, 10, Columbus Circle, New York 19, N.Y. 1957.

The *First Decade Report of the World Medical Association* should be compulsory reading for the Council of the B.M.A. and for all interested in the political problems of medicine. It is a mine of information set out clearly in 18 chapters with an appended index. Here can be found answers to the many questions asked about the W.M.A.: its history, what it is, how it is organized, what are its objects, what it has accomplished and hopes to accomplish, and how it is financed. Here is the fascinating story of how an idea born in B.M.A. House in 1945 became a fact in Paris in 1947, and how in the short space of ten years the W.M.A. has become the recognized authority to speak for the doctors of the world in international affairs.

The report contains the Declaration of Geneva (a modern version of the Hippocratic Oath), the International Code of Medical Ethics, and the Twelve Principles of Social Security and Medical Care. There is an account of the First World Conference on Medical Education, held in London in 1953, and the plans for the second one, which will take place in Chicago in 1959.

Chapter I contains a very condensed account of the history of the W.M.A., and might with advantage have been expanded. Mention might have been made of Sir Hugh Lett, a past President of the B.M.A., who took the chair at the preparatory conference in B.M.A. House in 1946 and again at the first half of the meeting in Paris in 1947, and whose quiet dignity did much to ensure the success of those historic gatherings.

Study of Chapter V, which deals with the W.M.A.'s finances, may be difficult for the British reader, as the figures are given in Swiss francs and U.S. dollars, and so he may fail to appreciate how much the W.M.A. has depended, and still depends, on the United States Supporting Committee's contributions. In the first few years the U.S.A. provided about 90% and the rest of the world only 10% of the income of the W.M.A. Slowly over the years the proportions have become less unequal, yet the figures for 1956 appear to show a sum of approximately £36,800 as coming from the U.S.A. and £19,500 from all other member associations.

Chapter XII is an account of the work of the Social Security Committee, whose reports have always been a major topic at all meetings of the General Assembly. No subject is more interesting to doctors all over the world, who find their daily lives and professional work affected at so many points by the impact of the State or governmental agencies. Of necessity this chapter can only hint at the volume of work done by the committee, which has produced many valuable reports and surveys. In this country, as in many others, great interest is taken in the various schemes of medical care operating in the different countries of the world. It would have helped if references could have been given in this chapter to the dates when the reports and discussions were published in the *World Medical Journal*.

Those closely connected with the W.M.A. will read this report with considerable pride, and it will bring back a host of memories—of old friends, extremely hard work, hot discussions conducted in three languages going on to midnight, wonderful hospitality, long tiring journeys across half the world, but most of all of a tiny group sustained by faith in an ideal. This ideal is to sustain and increase the importance of the W.M.A. in order to foster the essential unity of doctors all over the world—doctors differing in language and culture and in many other ways but united in their service to mankind irrespective of creed or colour or politics; and to educate, encourage, and assist them in the struggle to preserve their professional traditions from encroachment by many hostile forces.

J. A. PRIDHAM.

ANALGESIA IN CHILDBIRTH

Inhalation Analgesia in Childbirth. By E. H. Seward, M.A., D.M.(Oxon), F.F.A. R.C.S., D.Obst.R.C.O.G., and R. Bryce-Smith, M.A., D.M.(Oxon), F.F.A. R.C.S. (Pp. 58+viii. 7s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

The conduct of analgesia in childbirth, in this country at all events, is by and large in the hands of midwives. The quality of their service rendered to the community depends not only on their technical skill and on the availability of the necessary equipment but on the understanding by the midwife of the physiological problems involved. The previous literature on this subject aimed at the midwife tends to stress the technical details of using the various inhalers to the virtual exclusion of any consideration of the pharmacological actions of the drugs concerned, the physiological basis for analgesia in labour, or even the importance of the correct emotional rapport between midwife and patient. This little book attempts to do all these things. To do it in 58 pages is patently impossible. Like so many others, the authors have had to choose a middle path between brevity in words and a small cheap book, and completeness and an expensive bulky one. The result is an acceptable booklet, within the reach of every pocket, which will teach the midwife all she needs to know about the real problems of analgesia and about the use of nitrous oxide and "trilene" in overcoming them. Doctors, too, who may be called upon to administer analgesia, and perhaps even to teach this art to others, will read this book with pleasure and profit.

W. W. MUSHIN.

5-HYDROXYTRYPTAMINE

5-Hydroxytryptamine: Proceedings of a Symposium held in London on 1st and 2nd April, 1957. Edited by G. P. Lewis, Ph.D. (Pp. 253+xvii; illustrated. 60s.) London, New York, Paris, Los Angeles: Symposium Publications Division, Pergamon Press. 1958.

Symposia are held very frequently in the United States, and the practice of holding them is increasing in this country. Sometimes they are held when new work has been published so that this can become more widely known and be discussed. Sometimes they are held, as this one was, when the subject is in a state of confusion, and it seems very doubtful whether such a symposium serves any useful purpose. Certainly so far as those not working in the field are concerned the account given in the book does no more than indicate how far those taking part were from any leading discovery.

The demonstration of the presence of 5-hydroxytryptamine in the brain was followed by Brodie's finding that reserpine, a tranquillizing drug, decreased the cerebral content of 5-hydroxytryptamine. This led Brodie to his hypothesis concerning the role of this substance in brain. But, as Dr. Marthe Vogt pointed out, the evidence is conflicting. If hydroxytryptophan is given by mouth it leads to an increase of hydroxytryptamine in the brain, and in the presence of iproniazid (to preserve this hydroxytryptamine from destruction) there is excitement. But there is also an increase of hydroxytryptamine in the brain after giving phenytoin, which is an anticonvulsant, and then the effect is not excitement but sedation.

Much work has been done by finding antagonists to hydroxytryptamine on tissues like the rat uterus and then determining their effect on the state of lethargy produced in a cat by injecting hydroxytryptamine into the lateral ventricle. Since L.S.D. (lysergic acid diethylamide) is a powerful antagonist of hydroxytryptamine on uterine muscle it was thought that the hallucinations which L.S.D. causes might be due to antagonism of hydroxytryptamine

in the brain. Dr. Vogt described evidence favouring the view that the antagonistic effects of hydroxytryptamine and L.S.D. on behaviour do not depend on simple interaction by competition in the brain, but on selective sensitization of a characteristic group of centres by each drug. A protest should be made about the price of £3 charged for this small book.

J. H. BURN.

OBSESSIONAL NORDIC MAN

A Theory of Disease. By Arthur Guirdham, M.A., D.M., B.Sc.(Oxon), D.P.M. (Pp. 204. 21s.) London: George Allen and Unwin Ltd. 1957.

If the simple purpose of Dr. Guirdham's book was evangelical, if he intended to spread the Buddhist philosophy, to teach contemplation, non-attachment, the control by Yoga of the autonomic nervous system, Oneness and the merging of the You that is not You into the Absolute—then his book would have had a certain appeal for the Westerner, even for doctors who are "hot for certainties." For Nordic man, suffering from *angst* for 25 years and not a little guilt feeling for the last 15 years, might be persuaded that his obsessional activity had, in the modern idiom, done him a lot of no-good. He is more than a little bewildered by the failure of the politicians and economists to agree on the cause of, and to find a cure for, such common disorders as inflations and recessions; he is alarmed by the possible effect of radioactivity on the genes of his children and grandchildren; and he is disturbed by the rapid advance of mental disorder and neurosis, and by no means unmindful of the incidence of such diseases as duodenal ulcer and coronary thrombosis. Speaking in a medical sense only, he might be persuaded to follow the way of health if he were convinced of his true direction. But the medical black sheep, looking up to Dr. Guirdham, will remain unfed. "Health," he says in his introduction, "is the incidental product arising from the process of self-annihilation." The sick man who seeks health through the Buddhist philosophy "is encumbered by an awareness of self" and is therefore unlikely to be successful in his search.

Dr. Guirdham takes the Freudian theories of repression and the unconscious and extends them to the conclusion that the three types of disease—neurosis, functional (autonomic) disorders, and organic stress diseases—result from a repression of emotion into three strata, differing in depth, of the unconscious mind. This theory appears to be supported by little enough evidence; indeed, throughout the book the factual basis for Dr. Guirdham's theories is not considerable. He finds it easier to believe, for example, that the high incidence of poliomyelitis in North America, in Scandinavia, and Great Britain is related to Protestantism and agnosticism rather than to our hygienic habits. He should find further support for his belief in the paper, referred to recently by an American correspondent in another medical journal, in which a statistical association was demonstrated between toxaemia of pregnancy and the Baptist faith.

Mechanistic medicine at least makes no claim to be a guide to the life of the spirit; it is a pity that Dr. Guirdham's unscientific medicine prevents a proper appreciation of his philosophy. Eastern religion, however, makes no profound appeal to Western man; self-annihilation appears to him to be but a form of self-preoccupation. And so far as Yoga is concerned, all his physiological knowledge, acquired from the day of Claude Bernard onwards, persuades him that nature intended the autonomic nervous system to be the forgotten nervous system. Although Yoga may be a good treatment for the patient with a visceral neurosis, it would be travelling backwards in time for the healthy to acquire again the conscious mastery of the autonomic nervous system.

If the concentration camps came again it would be useful to have taught oneself the inhibition of afferent stimuli, whether of pain, discomfort, or indoctrination; but to lie in the bath and aspirate the bath water into the colon would seem to hold few advantages for Western man.

"You are old, Father William," the young man said,
"And your hair has become very white,
And yet you incessantly stand on your head.
Do you think, at your age, it is right?"
"In my youth," Father William replied to his son,
"I took in fresh air through my nose,
But now that I find that my colon gets none
I supply all its needs in this pose."

Perhaps all that obsessional Nordic man needs is to recover his sense of fun, to laugh at himself again in Alice's Looking Glass.

D. V. HUBBLE.

CLINICAL PROCTOLOGY

Essentials of Clinical Proctology. By Manuel G. Spiesman, M.D., F.S., L.L.D., F.I.C.P., and Louis Malow, M.D., B.S., F.A.C.S. Third edition. (Pp. 316+viii; illustrated. $8.75.) New York and London: Grune and Stratton. 1957.

Clinical Proctology. By J. Peerman Nesselrod, B.S., M.S., M.Sc.(Med.), M.D., F.A.C.S., F.A.P.S. Second edition. (Pp. 296+xix; illustrated. 49s.) Philadelphia and London: W. B. Saunders Company. 1957.

The authors of the first of these two books concern themselves with an account of all the minor diseases of the rectum and anal canal which come within the sphere of the true specialist proctologist. This type of specialist, confining his attention to the more minor conditions in the rectum only, does not exist in Britain, so that the surgeon with interests in proctology may well find this book too limited in its scope, whereas the general practitioner may find it too detailed and confusing for his taste. It falls between the two proverbial stools. For example, but a paragraph is devoted to the surgical treatment of cancer of the rectum, whereas the treatment of polyps is fairly extensively examined. Again, the surgeon can hardly be satisfied with the cursory description allocated to Hirschsprung's disease, whilst the general practitioner will probably consider excessive the 20 pages devoted to the study of the pecten band, the existence and importance of which will still be contested by its antagonists. The book includes a chapter on the anatomy of the region and a useful summary of congenital abnormalities.

The second book also limits its field to the study of those conditions of the rectum which may be treated locally. Its opening chapters, after examining the anatomy of the region, concern themselves to a considerable extent with advice to the clinician as to how to deal with a patient undergoing a proctologic examination. Though these are valuable, one feels that they would be better learnt by the postgraduate student during instruction in his clinical work rather than from the comfort of his armchair. The technique of many minor operations is described in valuable detail, and sections are devoted to careful concern with pre- and post-operative care. Selected bibliographies are included at the end of each chapter.

STANLEY AYLETT.

A volume in honour of Dr. P. H. Andresen, on the occasion of his sixtieth birthday, has been published by Ejnar Munksgaard, Copenhagen (200 pages; 38 Danish kroner). Dr. Andresen is chief of the municipal blood banks in Copenhagen, and the contributions, principally in English, consist of papers on haematology and related subjects.

J. T. Irving's *Calcium Metabolism*, one of the series of Methuen's monographs on biochemical subjects (177 pages; 11s. 6d.), discusses all aspects of the subject, from the ingestion of calcium to its final excretion from the body. It is concerned principally with human metabolism, although experimental work in other mammals and in birds is also described. There are comprehensive lists of references and a good index.

The sixth edition of Blacklock and Southwell's *Guide to Human Parasitology for Medical Practitioners* has been revised by Professor T. H. Davey. It is published by H. K. Lewis and Co. Ltd., London (222 pages, illustrated; 30s.).

BRITISH MEDICAL JOURNAL
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THE ORIGIN OF SPECIES

On July 1, 1858, a paper was read to the Linnean Society briefly describing Charles Darwin's views on the origin of species: this was a year before the publication of his great work. But Darwin's name was not the only one attached to this paper, because his friend, A. R. Wallace, had come to similar conclusions independently, and the communication to the Linnean Society was a joint one. Elsewhere in this issue (p. 1538) F. N. L. Poynter describes the events which led to the reading of this paper and to the subsequent revolution in biological thought. It has sometimes been said that Charles Darwin was the founder of scientific biology, and, while admirers of Harvey, Linnaeus, Spallanzani, and of many others might demur, there is a sense in which it is true. It is, however, more important to realize that he was the last of the series of creators of science than that he was the first representative of a new biology. The four hundred years that separated the birth of Copernicus from the publication of the *Descent of Man* had seen scientific method applied with increasing confidence born of success to a wide variety of cosmic and terrestrial processes, but man himself was exempt. Profane philosophers, sceptical historians, and scientific physicians may have had few illusions about man's nature, but so long as his origins remained obscure the whole of science was on probation. It certainly provided a method of increasing our understanding of nature, but not necessarily the only method; for, if the prevailing pre-Darwinian conceptions of man were valid, then inspiration from supernatural sources was a possible, and in principle more reliable, path to exact knowledge.

By establishing the fact of evolution and by providing a wholly rational explanation of how it had occurred, Darwin's work led inevitably to a realization of the animal origins of mankind. This, in turn, could only remove all inhibitions from the study of man, and with them went the last intellectual barriers to the application of scientific method. From Darwin's day onward nothing at all remained immune from scientific inquiry. The foundations of science were completed. His work was therefore of more than parochial interest to biologists: it was a justification, in retrospect, of all that science had attempted. Yet, although the Darwin–Wallace paper, the *Origin of Species*, and the *Descent of Man* can now be seen as the consummation of the humanist impulse of the Renaissance, their publication had equivocal implications for biology. For many years afterwards biologists were preoccupied with Darwinian studies of a particular kind—the reconstruction of the evolutionary genealogies of all known animals, living or extinct. This was fascinating and necessary work, requiring for its success the sort of minds that make first-class lawyers. But if the methodology was legal the method was anatomical, and the impetus given by Darwin to comparative anatomy led, in the event, to a partial neglect of physiological and other experimental approaches to living material. For this, it may be added, Darwin himself cannot justly be held responsible. He was remarkable, even in his day, for the catholicism of his biological interests, and, though obsessed by his own researches, he did not demand that others share his enthusiasm for them.

It was inevitable that the experimental biologists should emancipate themselves from what they felt to be the stifling effects of a post-Darwinian orthodoxy, and perhaps it was only natural that in doing so they should underestimate the value of Darwin's work. Unfortunately, however, this reaction coincided with the renewed interest in problems of inheritance and variation that followed the rediscovery, little more than fifty years ago, of Mendel's findings. The early neo-Mendelians found themselves out of sympathy both with Darwin's own views on heredity and with the role he assigned to natural selection in the evolutionary process. For two decades Darwin's influence in biology was minimal. It is significant that when the centenary of Darwin's birth was celebrated in 1909 the commemorative volume produced for the occasion had about it a slight air of puzzled piety. Many of the contributors seemed to have difficulty in relating Darwin's work to the subject of their essays, and one or two made frankly no attempt.

This year, as we celebrate the centenary of the Darwin–Wallace paper, the situation is much changed. While such tributes as *A Century of Darwin*,[1] it is true, confine themselves to those aspects of biology upon which Darwin himself touched, they reveal that in these fields his ideas still live and have relevance to present-day inquiry. This is, perhaps, most striking in the case of genetics. Genetics came to terms with Darwinism some thirty years ago, and adopted the designation "neo-Darwinism." This now proves to have more meaning than was once thought, since in recent years genetical research has

[1] *A Century of Darwin*, edited by S. A. Barnett, 1958. William Heinemann Ltd., London. Price 30s.

reopened the experimental study of problems, including natural selection and sexual selection, which, so far as hard facts were concerned, had remained much as Darwin left them. It would be very rash to assume that we have yet extracted from the enormous body of Darwin's labours as a biologist all that can be of use to us.

THE E.C.G. IN DIAGNOSIS

If the body were a homogeneous sphere, the heart a single electrical cell in the centre of the body, and the electrochemical composition of the heart cell known, electrocardiography could be reduced to an exact physical science. The heart, however, consists of a series of chambers the walls of which are composed of a syncytium of cells, its position in the body is eccentric, the conducting tissue of the body is heterogeneous and of no convenient geometrical shape, and the electrochemical composition of the heart cells is incompletely understood. While, therefore, certain general physical laws may be applied to the analysis of the electrocardiogram, electrocardiography remains essentially an empirical science.

The use of the electrocardiogram, as a clinical test, has been much extended during the last two decades. The test is simple to perform and is now regarded as a routine hospital investigation ; in many of the larger hospitals as many as 5,000 to 10,000 electrocardiograms are recorded yearly. Now L. G. Davies,[1] writing on variation among observers in their reports on electrocardiograms, has raised the question of accuracy of these reports and of the extent of the reliability of the test in diagnosis. Davies submitted 100 electrocardiograms for report to ten different observers, nine of whom had a special interest and experience in cardiology. No clinical details of the patients were given and only one of three reports was allowed—normal, infarction, or abnormal. The last report covered all diseases of the heart other than cardiac infarction, such as right and left ventricular hypertrophy, myxoedema, pericarditis, disturbances of electrolyte balance, and so on. The same series of electrocardiograms was circulated to each of the reporters twice at an interval of not less than a fortnight. The investigation disclosed not only wide variation between the different observers but also a considerable variation between the first and second reports of individual observers on the same electrocardiograms. The reporter who showed the greatest inconsistency with himself and variation with the reports of others was the general physician with special interests outside cardiology.

The observer variation among the nine experienced observers with a special interest in cardiology was analysed. On 29 out of 100 electrocardiograms a unanimous report was given ; on 49 electrocardiograms there was a two-thirds majority ; on the remaining 22 electrocardiograms less than a two-thirds majority was found ; and on some tracings opinion was almost evenly divided. In addition, the inconsistencies between the first and second reports of the same observer varied between 7 and 33 out of the 100 electrocardiograms reported.

An investigation which aims to estimate the accuracy of a particular test does so best if it reproduces the circumstances under which the test is usually made. In Davies's study not all the conditions conformed to those of routine electrocardiographic reporting. First, only a restricted range of reports was allowed and no heading, such as "doubtful infarction, but possibly normal," or "abnormal, possibly infarction," was included. Secondly, no opportunity was offered to repeat the electrocardiogram in a doubtful case, or to see whether serial changes helped to establish the diagnosis, or to carry out an exercise electrocardiogram in a patient whose resting electrocardiogram was borderline. Thirdly, no clinical details of the patients were given to the reporters, such as the age and sex of the patients, their blood pressure, and whether they were having digitalis. These details are usually given to those reporting on electrocardiograms and must to a certain extent sway them in making their report. Fourthly, the term "infarction" is differently interpreted by different physicians, some allowing only macroscopic infarction and others including ischaemic heart disease in general. Had the conditions of normal electrocardiographic reporting been reproduced in the investigation, it is likely that a higher degree of agreement would have been reached between different observers. The inconsistencies in reports of individual observers are more worrying, but they probably indicate doubt in the mind of the reporter and might have been considerably lessened if a borderline report of "doubtful" had been allowed. But some inconsistencies would almost certainly have remained, and these must reflect the extraordinary complexity of the modern electrocardiogram, with six, nine, or even 12 leads to be analysed in one graph.

Davies's study emphasizes the need for a proper understanding of what the electrocardiogram can offer as an ancillary diagnostic aid. It underlines some of its limitations, and shows that a single resting electrocardiogram, interpreted without knowledge of the clinical details of the patient, ought not to be expected to provide the diagnosis. It also emphasizes the need for special experience in cardiology in those

[1] Davies, L. G., *Brit. Heart J.*, 1958, **20**, 153.
[2] Paton, B. C., *Amer. J. Med.*, 1957, **23**, 761.

reporting on routine electrocardiograms. None, however, would doubt the great value of the electrocardiogram as a diagnostic tool correctly used, and this is borne out by B. C. Paton[2] in a recent study of 266 necropsies on patients dying in hospital from cardiac infarction. He found an accuracy rate of diagnosis of only 44% in the group as a whole; in those cases in which an electrocardiogram had been recorded, however, the accuracy rate of diagnosis was 94%, while the remaining 6% showed electrocardiograms compatible with, though not diagnostic of, cardiac infarction.

AETIOLOGY OF TRACHOMA

Trachoma, with its world-wide distribution and history going back to classical antiquity, is still an aetiological puzzle, even if not quite the therapeutic problem it has been for centuries. At one time emphasis was laid on its concentration along the Mediterranean littoral, and some over-simple deductions were drawn from this. In contrast, racial susceptibility or lack of susceptibility was postulated to explain poorly authenticated variations in the frequency of the affection among different populations; quite erroneously the Negro, in particular, was regarded as unsusceptible to trachoma. With fuller knowledge it became clear that trachoma is met wherever poor sanitary conditions and overcrowding create the necessary conditions for its spread. Trachoma is not racial or climatic but one of the classical diseases of poverty; its perpetuation is ensured wherever adequate facilities for treatment are lacking, and its infective nature has been assumed for some decades now. In an impressive monograph—his penultimate effort—H. Noguchi[3] in 1928 recorded that in five cases of trachoma in American Indians in Arizona he had isolated a hitherto unknown bacillus which he considered causative of trachoma and designated "*Bacterium granulosis*." The standing of Noguchi compelled serious attention to this claim, though further studies in Indian reservations and elsewhere showed that the newly isolated organism was not the cause of trachoma, but of a follicular reaction of the conjunctiva.

This failure to establish a bacterial cause for trachoma proved a turning-point in the quest for pathogens: increasing attention was now being given to the inclusion bodies described by L. Halberstaedter and S. von Prowazek[4] in 1907 in their classical studies in Java. They went there to investigate syphilis, but paid some attention to trachoma as a side-issue, and in this subsidiary study they uncovered a cellular reaction which is one of the foundations of the modern study of virus infections. They themselves held that some of the granules of these inclusion bodies contained the virus of trachoma. Search for this postulated virus has had a chequered career. For another decade or so after Noguchi's unsuccessful work the issue was still clouded by rather indeterminate work on inclusion bodies, which according to some observers were merely artifacts readily found in any conjunctival reaction. C. G. Pandit and his associates[5] in 1935 and A. Macchiavello[6] in 1944 claimed to have isolated a causative virus, and other workers have since also advanced such claims, none of which have, however, been confirmed. Last year F. F. T'ang and other Chinese workers[7] reported the isolation of a virus from patients with trachoma by inoculating conjunctival material into the yolk sacs of eggs containing embryos 6–8 days old; the egg-cultured virus produced a follicular conjunctivitis in rhesus monkeys, in one instance with inclusion bodies. Morphologically this virus resembled those of psittacosis and of lymphogranuloma. It was sensitive to penicillin, terramycin, and sulphacetamide in the experimental dosages used, and only feebly sensitive to aureomycin and chloramphenicol.

Work on trachoma has laboured under the difficulty that, except for some monkeys, no animal appears to be susceptible to infection with trachoma material, and inoculation in the rhesus and other monkeys is not altogether satisfactory. The difficulty is so real that the World Health Organization[8] has laid down the condition that "at the present time experimental trachoma cannot be diagnosed with certainty in hosts other than man." In assessing the claims advanced by the Chinese workers, L. H. Collier and J. Sowa,[9] of the Lister Institute in London, have confirmed in broad outline the morphology and other features of the virus isolated by T'ang and his associates and have done so on the basis of material collected from patients with trachoma in Gambia. What is of particular significance is that they have succeeded in producing experimental trachoma in a blind volunteer, the resultant lesion satisfying the clinical and histological criteria of experimental trachoma. Should this confirmation prove valid, the eradication of trachoma will at length become feasible.

[3] Noguchi, H., *J. exp. Med.*, 1928, **48**, Suppl. 2.
[4] Halberstaedter, L., and Prowazek, S. von, *Arb. Gesundh.-Amte (Berl.)*, 1907, **26**, 44.
[5] Pandit, C. G., Wright, R. E., Rao, R. S., and Satyanathan, *Indian J. med. Res.*, 1935, **23**, 475.
[6] Macchiavello, A., *Rev. ecuat. Hig.*, 1944, **1**, 211.
[7] T'ang, F. F., Chang, H. L., Huang, Y. T., and Wang, K. C., *Chin. med. J.*, 1957, **75**, 429.
[8] World Health Organization, *Tech. Rep. Ser.*, 1956, no. 106.
[9] Collier, L. H., and Sowa, J., *Lancet*, 1958, **1**, 993.

TREATMENT OF LEPTOSPIROSIS

In Great Britain, where only *Leptospira icterohaemorrhagiae* and *L. canicola* have been recorded, leptospirosis is a comparatively uncommon disease, though an investigation of piggery workers in Scotland made by J. D. Coghlan and colleagues[1] indicated that a certain number of cases pass unrecognized. In many other countries, however, where a wider variety of antigenic types exist, leptospirosis presents medical and veterinary problems of great importance. For instance, epidemics of infection by *Leptospira grippotyphosa* involving hundreds of agricultural workers have been reported from Germany[2] and from Israel.[3] In the ricefields of North Italy B. Babudieri and colleagues[4] found that about 50% of new workers developed leptospirosis, mostly due to *L. bataviae*, during their first year in the fields. In the military sphere D. G. Levis[5] recorded 291 cases, caused by a variety of serological types, among troops on jungle patrol in Malaya in 1954–5, and in one operation in Viet Nam 126 men, nearly one-quarter of the effective force, were incapacitated by the disease.[6] In the U.S.A. infection with *L. pomona* is widespread among cattle, and is an important cause of bovine abortions. According to E. V. Morse[7] the disease is probably responsible for an annual loss of 100 million dollars to the farming community.

Some forty or more antigenic types (serotypes or species) of leptospires are known to be pathogenic for man, but in the early stages of infection they all produce similar clinical features. The onset is usually sudden, with fever, often accompanied by shivering or rigors, headaches, muscular pains and tenderness, conjunctival injection, and prostration. As to later signs and symptoms, individual cases, even those caused by the same serotype, react in widely different ways. Broadly, the disease tends to present in one of three forms: (1) a severe type with marked signs of hepato-renal damage, of which classical Weil's disease may be taken as an example; (2) a type in which signs and symptoms of meningeal irritation are outstanding features, as in "swineherd's disease" caused by *L. pomona*; and (3) a type characterized by abdominal disturbances, as is commonly found in *L. grippotyphosa* infections. Except in the severe type, frank jaundice is not common, but in all forms some degree of renal damage is usually noted. It may appear only as a transient albuminuria, while at the other extreme the lesion may be so extensive as to lead to anuria and uraemic coma. It is therefore important to keep a close watch on the balance of fluid and electrolytes, and to correct these by intravenous infusions when necessary. If anuria develops, it is essential to institute the regime described by G. M. Bull[8] for the conservative treatment of anuric uraemia.

Many antibiotics have been used therapeutically, but, except in the case of penicillin, the numbers of patients treated have been too small to allow any valid conclusions to be drawn. And on the value of penicillin very divergent opinions have been expressed. J. C. Broom[9] reported that the death rate among 152 jaundiced cases of true Weil's disease treated with penicillin in various hospitals in England during 1947–50 was 22%, as compared with 23% for 103 jaundiced cases which did not receive the drug. A series of 67 patients in Puerto Rico, about half of whom were infected with *L. icterohaemorrhagiae*, were treated with various antibiotics, including penicillin, by H. E. Hall and colleagues[10]; when the results were compared with those from a control group of 12 who received no antibiotics the conclusion was reached that none of the antibiotics was effective. Similar disappointing results were obtained by A. C. Fairburn and S. J. G. Semple[11] with a course of 600,000 units of penicillin 6-hourly for five days in a smaller but carefully controlled series of cases caused by a variety of serotypes among Service personnel in Malaya. Completely opposite findings are reported by other workers. R. L. Doherty[12] analysed the results of treating 71 cases with penicillin in some Queensland hospitals. He considered that penicillin shortened the febrile period and ameliorated the patients' general condition, and that benefit was greatest in the group which received the highest dosage of 4,000,000 units daily.

Another extensive trial of penicillin in Malaya was recently described by J. Mackay-Dick and J. F. Robinson.[13] The series comprised 41 United Kingdom troops and 43 Gurkhas; treatment was begun as soon as a clinical diagnosis of leptospirosis was made, but the diagnosis in all cases included in the report was later confirmed by laboratory tests. None of these patients died, but no information is given about the outcome in cases which did not receive penicillin. Penicillin was given intramuscularly in a dosage of 600,000 units 4-hourly for 24 hours, and then 6-hourly for another six days. When treatment was started before the sixth day of illness, the pyrexial period was reduced and the patients quickly improved. Within a few hours of receiving the first dose of penicillin 70 of the 84 cases showed a Herxheimer reaction, which was regarded as an indication of a good response to treatment. Reactions of this type, followed by rapid relief of symptoms, have been described by some workers[14,15] but not by others. It is improbable that so many of the men in the Malayan series could be sensitive to penicillin, so the authors' suggestion seems the most likely explanation of the reaction. However, even if these claims for the efficacy of penicillin are accepted, the need for early institution of therapy needs emphasis. This entails accurate clinical diagnosis, which, in the absence of a clear history of exposure to risk of infection, may be difficult in sporadic cases.

[1] Coghlan, J. D., Norval, J., and Seiler, H. E., *Brit. med. J.*, 1957, **1**, 257.
[2] Popp, L., *Z. Hyg. Infekt.-Kr.*, 1950, **131**, 575.
[3] Olejnik, E., and Shneyerson, S., *Nature (Lond.)*, 1950, **166**, 526.
[4] Babudieri, B., Bussinello, E., Bajocchi, E., Salvi, A., and Massa, L., *Riv. Infort. Mal. prof.*, 1955, **42**, 453.
[5] Levis, D. G., *Proc. R. Soc. Med.*, 1957, **50**, 119.
[6] Lajudie, P. de, and Brygoo, E. R., *Méd. trop.*, 1953, **13**, 466.
[7] Morse, E. V., *Proc. Amer. vet. med. Ass.*, 1955, 162.
[8] Bull, G. M., *Lancet*, 1955, **1**, 731.
[9] Broom, J. C., *Brit. med. J.*, 1951, **2**, 689
[10] Hall, H. E., Hightower, J. A., Diaz Rivera, R., Byrne, R. J., Smadel, J. E., and Woodward, T. E., *Ann. intern. Med.*, 1951, **35**, 981.
[11] Fairburn, A. C., and Semple, S. J. G., *Lancet*, 1956, **1**, 13.
[12] Doherty, R. L., *Aust. Ann. Med.*, 1956, **5**, 23.
[13] Mackay-Dick, J., and Robinson, J. F., *J. roy. Army med. Cps*, 1957, **103**, 186.
[14] Covaleda, J., Pumarola, A., and Cantarell, I., *Rev. ibér. Parasit.*, 1953, **13**, 289.
[15] Crooks, J., and Blair, W., *Brit. med. J.*, 1955, **1**, 885.

HEAT ILLNESS

Manasses, the husband of Judith, died in the days of the barley harvest: "He stood over them that bound sheaves in the field, and the sun came upon his head, and he died."[1] The power of the tropical sun to cause illness or death has been feared for centuries by northerners, and even twenty-five years ago newcomers to the tropics were still solemnly warned of the danger of sunstroke. But, as the authors of the memorandum entitled "A Classification of Heat Illness," published at p. 1533 in this issue, point out, "ictus solaris" cannot be recognized as a distinct entity. When J. W. D. Megaw[2] wrote in 1939 that "the tropical sun does not damage the head and neck through any mysterious action of the ultra-violet rays, but by its powerful heating effect," he implied that "sunstroke" was really "heat stroke." Contemporary textbooks[3] of medicine called all heat illness "heat stroke," and four clinical types are mentioned: heat exhaustion, heat hyperpyrexia, the gastric type of illness, and the choleraic or gastro-intestinal type of illness. In spite of the fundamental work by K. N. Moss[4] and J. S. Haldane,[5] field observations made by J. H. Talbott,[6] and the experiments carried out by F. Marsh[7] at Abadan, some old ideas about heat disorders persisted even longer than did those outmoded prophylactic devices the spine pad and the cholera belt.[8] During and after the second world war, however, the problem of heat disorders was intensively studied by British,[9 10] Australian,[11] and American[12] workers, and the recent revision of the "International Statistical Classification of Diseases, Injuries, and Causes of Death"[13] reflects the early results of these studies. But even in this most recent classification "sunstroke" is still listed, and no proper provision is made for distinguishing between the various types of heat exhaustion.

Against this background a joint subcommittee of the Medical Research Council and of the Registrar-General's department began working on a new classification six years ago. The Services were consulted and also many of those who had worked in the field, so that the final memorandum represents an agreed statement in so far as it could be expressed within the rigid framework of the International Classification. The subcommittee is to be congratulated on its success not only in finding pigeon-holes for all the clinically recognizable varieties of heat illness but also in reconciling the inevitably divergent views of its consultants. A classification cannot be based solely on aetiology; clinical manifestations must also be considered, since it is on these that the initial diagnoses are made. This has led to some odd distinctions. Who, offhand, would care to distinguish between "heat stroke" and "heat hyperpyrexia"? In most textbooks the two are synonymous, but a distinction is made here on the speed of onset, development of coma, and body temperature. Another surprising distinction is between "salt deficiency exhaustion" and "heat cramps"; but this may be justified on clinical grounds. There will be some who will regret the spurious validity given to a highly controversial condition, "tropical neurasthenia," or, as it is called in the memorandum, "heat neurotic reactions." At least one author with long practical experience has suggested that the incidence of tropical neuroses is associated with the availability of psychiatrists to diagnose them.[14] Even if one accepts the possibility of a "hot climate fatigue," other factors besides heat are involved—for instance, in the Arabian desert it was said that the busier the group the less the incidence of this condition.

In the appendix to the memorandum thumbnail sketches are given of each of the major disorders. These brief clinical descriptions are admirable and should be most useful, but the authors invite criticism with their somewhat dogmatic statements on attribution. Much of what they say is acceptable, but sometimes the basic causes are barely touched upon, and the possibility that certain disorders may be "attributable to" endocrine factors is never even hinted at, although this has been suggested recently.[15] But a memorandum on such a controversial topic, though easy to criticize, must have been most difficult to write, and its publication at this moment is opportune. At the Tropical Medicine Congress next autumn it should be possible for the British and American groups to use this paper as a basis for discussion, and with the help of the other delegates to prepare an agreed and completely new classification for the 1967 edition of the International List.

[1] *Judith*, Chap. 8, v. 2.
[2] Megaw, J. W. D., *Hints on Health in India and Other Tropical Countries* (issued to new recruits to Colonial Service), 1938, London.
[3] Price, F. W., *A Textbook of the Practice of Medicine*, 1937, 5th ed., London.
[4] Moss, K. N., *Proc. roy. Soc. B.*, 1923, **95**, 181.
[5] Haldane, J. S., *Brit. med. J.*, 1923, **1**, 986.
[6] Talbott, J. H., *Medicine (Baltimore)*, 1935, **14**, 323.
[7] Marsh, F., unpublished reports to Anglo-Iranian Oil Co.
[8] Renbourn, E. T., *Med. Hist.*, 1957, **1**, 211.
[9] Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F., *Lancet*, 1944, **2**, 491, 527.
[10] Horne, G. O., and Mole, R. H., ibid., 1949, **2**, 279.
[11] Allen, S. D., and O'Brien, J. P., *Med. J. Aust.*, 1944, **2**, 335.
[12] Wolkin, J., Goodman, J. I., and Kelly, W. E., *J. Amer. med. Ass.*, 1944, **124**, 478.
[13] *Manual of the International Statistical Classification of Diseases*, 1957, W.H.O., Geneva.
[14] Ellis, F. P., *Lancet*, 1952, **2**, 527.
[15] Ladell, W. S. S., *Trans. roy. Soc. trop. Med. Hyg.*, 1957, **51**, 189.

RADIOLOGICAL DIAGNOSIS OF BREAST CARCINOMA

Diagnosis of carcinoma of the breast and estimates of the stage of the disease are made almost entirely as the result of clinical examination. *X*-ray examination of the breast has been little used, because it has not been thought capable of providing unequivocal information. At a few centres abroad, however, radiography has been used for this purpose. Several workers in the United States have described soft-tissue techniques for the radiological examination of the breast, and these were reviewed by N. F. Hicken and his colleagues[1] in 1938. Interest in the subject was revived by R. Leborgne,[2] of Montevideo, who described spiculated areas of increased density in cases of scirrhous carcinoma and punctate

[1] Hicken, N. F., Best, R. R., Hunt, H. B., and Harris, T. T., *Amer. J. Roentgenol.*, 1938, **39**, 321.
[2] Leborgne, Raul, ibid., 1951, **65**, 1.
[3] Baclesse, F., *J. Fac. Radiol. (Lond.)*, 1955, **6**, 145.
[4] Gershon-Cohen, J., and Ingleby, H., *J. Amer. med. Ass.*, 1958, **166**, 869.

calcification characteristic of duct carcinoma. F. Baclesse[3] has acknowledged the value of radiography in estimating the extent of a growth and in assessing prognosis. These findings, however, have chiefly served to confirm what was already suspected clinically. Recently J. Gershon-Cohen and H. Ingleby,[4] in the latest of several papers, have claimed that small and even unsuspected carcinomas can be demonstrated radiographically without the use of contrast media, and support this claim by reproducing the radiograph of an impalpable duct carcinoma less than 1 cm. in diameter. They point out that unsuspected carcinoma may be present in a tumour thought clinically to be benign, in a nodular breast with no predominant tumour, in a breast which feels normal, but of which the patient complains, and in a breast which feels normal and gives rise to no symptoms. Gershon-Cohen and Ingleby believe that radiological examination is essential in the first three groups. In their three-year survey of 1,500 patients with breast lesions there were 197 proved carcinomas: by radiology 135 of these had been correctly diagnosed, 46 had been suspected, and 16 had been misdiagnosed as benign. In 47 of these cases the lesion was judged clinically to be benign, and in 38 of these the authors state that further investigation and treatment stemmed from radiological examination. Only 9 cases out of the total of 197 were missed by both radiologists and clinicians. Moreover, the breasts of 1,102 apparently healthy volunteers were radiographed and four cancers were discovered—a finding which prompted Gershon-Cohen and Ingleby to advocate radiological examination of the breasts at the time of periodic medical examinations.

Early diagnosis is so important that a controlled study in this country to determine the validity of these results would appear to be well worth while. But growing awareness of radiation dangers underlines the need for prudence in selecting patients for radiological examination: periodic radiography of the breasts, even if practicable, is unlikely to be considered in Britain until the value of the method has been firmly established.

COST OF PRESCRIBING

The committee appointed a year ago, under the chairmanship of Sir Henry Hinchliffe, to investigate the reasons for the increasing cost of prescribing in the National Health Service in England and Wales (a parallel committee was appointed in Scotland under the chairmanship of Sir James Douglas) has made an interim report[1] at the urgent request of the Minister. A summary of it is printed at page 382 in this week's *Supplement*. The report is short and without detailed analysis of its subject, but the committee feels it has sufficient information to justify "a few comments and recommendations." Its first comment, "that so far we have found no evidence of irresponsibility on the part of doctors in prescribing," will be welcomed by a profession on whom those outside it, and knowing little of its problems, have been all too ready to lay the blame for the mounting drug bill. The report reminds its readers that the N.H.S. was not devised by the medical profession but by Parliament, and that it is a doctor's primary duty to restore and maintain his patients' health by using the therapeutic resources available to him. Nevertheless, however exacting their professional duties may be, doctors in the Health Service cannot escape, nor do they try to, a responsibility for the spending of public funds, and the recommendations in the Hinchliffe Committee's interim report are mainly aimed at providing practitioners with better information on how to achieve economy without sacrificing efficiency. It is suggested that medical students should be encouraged to refer to the *British National Formulary* and that more instruction than hitherto should be given in medical schools on its use. The committee recommends that the Minister should supply the alternative edition of the *Formulary*, which it particularly commends, to all clinical students, general practitioners, and hospital doctors, and, in agreement with the Association's evidence, it would like the prices of the items in it added. A doctor cannot discriminate between expensive and cheaper alternative drugs unless he knows the relative costs, and here the committee recommends that the Minister should confer with the B.M.A. and the Pharmaceutical Society with a view to producing a comprehensive prescribing handbook which would, among other things, supply this need. Also in line with its advocacy of more information for doctors is the committee's suggestion for a wider distribution of a more frequently published *Prescribers' Notes* in expanded form. In this connexion we may draw attention to the weekly column in the *Journal* on "To-day's Drugs."

The influence of advertising literature on doctors' prescribing costs inevitably figures in the report, and disappointment is expressed that certain firms still do not include the prices of their products. There follows the far-reaching proposal that manufacturers should be obliged by law to quote the retail price of their drugs in advertising material. The committee agrees with the B.M.A.'s view that the importance of the educative and advisory functions of regional medical officers is underestimated and recommends that proper incentives for men of the right calibre with experience in general practice to do this work should be offered. Not the least of a doctor's prescribing difficulties is the bewildering number of different names by which new drugs may be known. For example, there are just under 5,000 proprietary preparations available. A quicker evolution of approved names, as simple as possible, for new products would, the committee thinks, be one way out of this difficulty, and it would help approved names to compete more easily with the attractive ones coined by the drug firms for a place in the general practitioner's vocabulary. The British Pharmacopoeia Commission, therefore, is asked to review the principles on which it bases its selection of approved names. The committee, whose recommendations are much in line with the Association's evidence,[2] is continuing its task.

[1] Ministry of Health, *Interim Report of the Committee on Cost of Prescribing*, 1958. H.M.S.O., London.
[2] *Brit. med. J., Supplement*, 1958, 1, 126.

A CLASSIFICATION OF HEAT ILLNESS

A MEMORANDUM PREPARED FOR THE CLIMATIC PHYSIOLOGY COMMITTEE OF THE MEDICAL RESEARCH COUNCIL*

There is much confusion in the nomenclature at present applied to the various disorders resulting from exposure to hot environments, whether the latter occur naturally (as in the tropics) or artificially (as in industry). Part of this confusion arises from the use of such vague and unqualified terms as "heat exhaustion," "heat fatigue," and "heat collapse" that are applied indiscriminately to a wide range of syndromes. Even the term "heat stroke," which describes a clear-cut entity, has come to have a much wider connotation, and "sunstroke" is still used for different syndromes ranging from the potentially fatal hyperpyrexia in the desert to syncope on a summer's day. The nomenclature has been further complicated by the introduction of a variety of titles for the recently defined syndrome associated with anhidrosis following prickly heat, and for the more precise descriptions of the syndromes with predominantly neurasthenic symptoms.

Some of the confusion has also arisen from a failure to appreciate the environmental, physical, and physiological factors concerned in the production of heat-effects syndromes. A better understanding of these factors would help towards more exact diagnosis, prevention, and correct treatment, and help to solve outstanding problems. Also, without an adequate nomenclature statistical returns of the incidence of heat illness, for whatever purpose, are of little value.

Revision of Nomenclature

A thorough revision of the nomenclature has been prompted by increasing general appreciation of the inadequacy of the current nomenclature; by a request in particular from the Royal Naval Personnel Research Committee for a review of the problem; and by a suggestion that the relevant section of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*" (W.H.O.) needed revision. The matter was referred to the Climatic Physiology Committee of the Medical Research Council, and it was decided that an attempt should be made to devise a nomenclature that would satisfy these demands.

In a first draft memorandum a schedule of heat disorders was drawn up giving brief clinical descriptions of 14 disorders which are well recognized and documented (these are outlined in the Appendix). To cover the various grades and varieties of heat illness encountered in the literature a nomenclature of 22 terms was tentatively put forward. It was recognized that this was perhaps unduly elaborate and detailed. Subsequent criticism showed that a shorter classification was generally favoured. The discussions have revealed quite clearly that even those who would prefer broader classifications recognize these 14 "primary" disorders in their suggestions for regrouping. Indeed, the different systems of grouping which have been proposed as alternatives to the classification can be compared and made comprehensible only in terms of a basic list such as has been specified.

After much discussion with potential users, including representatives of the Royal Navy, Army, Royal Air Force, the Registrar-General's Department, representatives of the Council of the Royal Society of Tropical Medicine, and others, fair agreement has been reached on the nomenclature, coding, and categories listed in Table I. Eleven categories are distinguished, but all 14 disorders are actually named.

TABLE I

Title	I.S.C. No.*	Modified No. (for Processing but not for Publication of Statistics)
Heat stroke } Following anhidrosis, febrile illness, or unqualified	N 981.0	N 981.0
Heat hyperpyrexia } Following anhidrosis, febrile illness, or unqualified	N 981.5a	N 981.0
Heat cramps	N 981.2	N 981.2
Heat exhaustion:		
1. Anhidrotic	N 981.3a	N 981.6
2. Salt-deficiency (excluding heat cramps)	N 981.3b } N 981·3	N 981.7
3. Unqualified (including water-deficiency heat exhaustion, exercise-induced heat exhaustion, and heat syncope)	N 981.3c } N 981·3	N 981.3
Sunburn	N 981.4	N 981.4
Prickly heat	714.0a	N 981.8
Anhidrosis	714.0b	N 981.9
Heat neurotic reactions (including chronic heat neurotic reaction, chronic heat fatigue, mild asthenic reaction, mild heat fatigue)	318.3a	318.3 (part)
Other heat effects (including heat oedema)	N 981.5b	N 981.5

* In accordance with the codes of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* relating to heat illnesses (1957, W.H.O., Geneva).

Two sets of code numbers are given. The first is in complete conformity with the present numbers of the *International Statistical Classification.* The modifications and additions are shown, not by numbers, but by means of letters, as required by international recommendation. The number N 981.1 has been omitted, since the term "sunstroke," which occupies this number in the international classification, is not now recognized as a distinct entity. The international classification for the time being makes it possible for this term, although obsolete, to be used. The numbers in the second column are intended for private or departmental use only and *are not to be quoted in any* publication of statistics, for the reason that N 981.6 to N 981.9 are not officially a part of the international classification. However, they do not conflict with that code, as they are unallocated numbers. They enable four-figure sorting to be done, as is commonly the practice in making sickness returns. The present international classification of heat illness is given in Table II. It will be seen that the new proposals represent a logical expansion of the international scheme.

TABLE II.—*Heat Illness: International Statistical Classification (Existing List from the "Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.")*

N 981.0	*Heat stroke, except sunstroke*:—Heat apoplexy; heat stroke; thermoplegia
N 981.1	*Sunstroke*:—Ictus solaris; insolation; siriasis; sunstroke; thermic fever
N 981.2	*Heat cramps*:—Heat cramps
N 981.3	*Heat exhaustion and collapse*:—Heat collapse; heat exhaustion; heat prostration; heat syncope
N 981.4	*Sunburn*:—Actinic dermatitis; sunburn
714.0	*Diseases of sweat glands*:—Anhidrosis; heat rash; miliaria rubra; prickly heat; other diseases of sweat glands
318.3	*Asthenic reaction*:—Asthenic reaction; nervous debility; nervous exhaustion; nervous prostration; neurasthenia; psychogenic asthenia; psychogenic general fatigue
N 981.5	*Other*:—Excessive heat; heat effects not otherwise specified due to hot weather or overheated places

*The Climatic Physiology Committee set up a Subcommittee on the Nomenclature of Heat Illness (jointly with the Advisory Committee on Medical Nomenclature and Statistics of the General Registry Office). The membership of the Subcommittee was: Mr. R. M. Blaikley, Dr. O. G. Edholm, Dr. G. O. Horne, Dr. W. P. D. Logan, Dr. R. K. Macpherson, Dr. A. H. T. Robb-Smith, and Dr. J. S. Weiner (convenor). Various aspects of the memorandum were discussed by this Subcommittee, who also had the benefit of the views of the following, to whom acknowledgment is gratefully made: Surgeon Commander F. P. Ellis, Surgeon Commander J. M. Holford, Colonel W. D. Hughes, Dr. W. S. S. Ladell, Professor B. G. Maegraith, Group Captain W. P. Stamm, Professor A. W. Woodruff, and Dr. C. H. Wyndham. Surgeon Commander Ellis very kindly transmitted views from a number of American physiologists and climatologists.

The memorandum was prepared for the Subcommittee by Dr. J. S. Weiner and Dr. G. O. Horne.

Some Comments

The proposed classification represents a compromise, but it is believed it will satisfy the requirements of most users. The next revision of the *International Statistical Classification* is not due till 1967, so there is time for experience to be gained of the usefulness of these proposals and for new suggestions to be brought forward.

The classification, as already mentioned, is essentially a clinical one. It is, of course, feasible to construct a classification on the basis of aetiology or pathology (or a combination of both), and the proposed scheme could be reorganized along such lines.

It may be useful to comment here on various criticisms and queries to which the proposed classification has given rise.

The distinction between "heat stroke" and "heat hyperpyrexia" is somewhat arbitrary. "Heat stroke" should be confined to the syndrome in which the word "stroke" indicates the occurrence of severe disturbances such as convulsions or coma. It is suggested that "heat hyperpyrexia" should be used when there is a high body temperature (above the arbitrary level of 106° F.—41° C.), but with none of the dramatic accompaniments of heat stroke. The international classification does not specify "heat hyperpyrexia" (though this is a common clinical term), and in order to ensure that all cases are in fact notified it seems safer to specify both terms.

The term "heat exhaustion" is used by a number of writers on tropical medicine to mean "salt-deficiency heat exhaustion," and it was suggested that this restricted usage should be encouraged. However, this use of the term "heat exhaustion" is confined to a minority, and it was felt that unless the various categories of heat exhaustion are qualified in the way suggested the simple term "heat exhaustion" will continue to be misunderstood.

The distinction between "heat cramps (N 981.2)" and "salt-deficiency heat exhaustion (N 981.3b)" is not defensible on aetiological grounds. As is the case with "heat hyperpyrexia," the international classification does not separately specify the more general condition of "salt-deficiency heat exhaustion." In order to ensure the identification of all cases, with or without cramps, while maintaining the present system of coding, both terms need to be specified. There is also a body of opinion which believes that "heat cramps," being more easily recognized, should continue to be separately reported as a reliable index of the existence of salt deficiency.

The category "heat exhaustion (unqualified) (N 981.3c)," which contains three types of disorder, exemplifies the difficulty of arriving at subdivisions satisfactory to everyone. There are circumstances in which these disorders are particularly in evidence. In mining and other hot industries simple "heat syncope" and "exercise-induced heat exhaustion" provide by far the bulk of the cases of heat disorder. To these may be added cases of "water-deficiency heat exhaustion" which occur in men undergoing military training in hot regions due to insufficient drinking or provision of water. Yet to separate these three categories is regarded by some as making the whole classification too unwieldy. Since these conditions are not provided for in the present international classification it is thought that for the time being this category, multiple though it is, represents a definite improvement.

The term "heat neurotic reactions" has not previously been given prominence in classifications of heat disorder, but there is general agreement regarding the importance of specifying these conditions in a comprehensive scheme. Although there was not complete agreement on the best term to use, the majority were willing to accept "neurotic" rather than "neurasthenic" or "fatigue" to denote the psychological element. It should be added here that the mild form of this condition is not without its importance in industry; and in the Services, where individuals unacclimatized to heat are expected to carry out skilled work in warm environments, there are conditions which lead to complaints and ill-defined absenteeism. This is an instance where the classification serves purposes wider than that of hospitalization.

To indicate the severity of a heat disorder some writers have drawn a distinction between "exhaustion" and "collapse," using the latter term where the patient has in fact experienced a faint or a fall or is not ambulatory on arrival. There seems little reason to object to this, provided the type of collapse or exhaustion is always given the recommended adjectival qualification. In the proposed scheme all cases of collapse are to be included under "exhaustion."

It should be stressed that this or any other classification necessarily embodies much oversimplification. Various conditions merge into each other, and some have common features leading to overlap in symptomatology. In some areas where heat disorders occur the clinician may also deal with mixed cases. After allowances are made for the arbitrariness of certain subdivisions already mentioned—that between "heat stroke" and "heat hyperpyrexia" and between "heat cramps" and "salt-deficiency heat exhaustion"—it can be claimed that the various designated heat disorders do reflect differences of pathogenesis sufficiently to make them clinically distinguishable.

APPENDIX. SCHEDULE OF HEAT DISORDERS

Heat Stroke.—Attributable to failure of the heat-regulating mechanism. Characterized by very high body temperature and profound disturbances, including delirium, convulsions, and partial or complete loss of consciousness. The skin is dry and hot. May be of sudden onset, or there may be a prodromal period. May occur following known generalized anhidrosis (as in anhidrotic heat exhaustion), during the course of a pyrexial illness, or for no apparent reason apart from heat stress. High mortality.

Heat Hyperpyrexia.—Attributable to impaired functioning of the heat-regulating mechanism, but without characteristic features of heat stroke. Arbitrarily defined as a temperature above 106° F. (41° C.). May occur following known generalized anhidrosis (as in anhidrotic heat exhaustion), during the course of a pyrexial illness, or for no apparent reason apart from heat stress. May proceed to heat stroke.

Heat Cramps: "Miners' Cramp"; "Stokers' Cramp."—Attributable to salt deficiency in a hot environment. Painful spasms of voluntary muscles, usually following muscular activity and often precipitated by drinking unsalted water. May be accompanied by other evidence of hypochloraemia. Relieved by administration of salt.

Anhidrotic Heat Exhaustion: "Heat Exhaustion, Type II" (Ladell, Waterlow, and Hudson, 1944); "Tropical Anhidrotic Asthenia" (Allen and O'Brien, 1944); "Thermogenic Anhidrosis" (Wolkin, Goodman, and Kelley, 1944); "Anhidrotic Heat Exhaustion" (Horne and Mole, 1950).—Attributable to "chronic" sweating deficiency, nearly always preceded by severe prickly heat; usually associated with characteristic skin changes. Symptoms present occasionally at rest, especially if area of sweating deficiency is large and if in a very hot environment; symptoms aggravated by exposure to heat, and especially by exertion in heat. General physical and/or mental asthenia (loss of energy, initiative, and interest; irritability; difficulty in concentration, working, and sleeping). Under heat stress, aggravation of these symptoms, with intense feeling of warmth, dyspnoea, tachycardia, and distress, sometimes polyuria (stage of "exhaustion"); eventually collapse with transient loss of consciousness, unless heat stress removed; possibly proceeding to hyperpyrexia and even heat stroke. On examination after exposure to heat stress, skin dry except usually the face (which may be sweating profusely) and palms, soles, and axillae. The skin has a characteristic

appearance and feel; there may be pyrexia, depending on environment and duration of exposure to heat stress. Very slow return to normal sweating (many weeks).

Hypochloraemia: Salt-deficiency Heat Exhaustion, "Heat Exhaustion, Type I" (Ladell, Waterlow, and Hudson, 1944).—Attributable to inadequate replacement of salt loss in a hot environment, leading to dehydration and reduced blood volume. Symptoms and signs are similar to hypochloraemia under ordinary environmental conditions. May be "chronic," with general asthenic symptoms—that is, exhaustion—or "acute," with collapse, pallor, sweating, vomiting, and sometimes muscle cramps; urine very scanty, concentrated, and almost or quite free from chloride; haemoglobin concentration and plasma protein raised. Sometimes fatal. Relieved by restoration of blood chloride.

Water Deficiency Heat Exhaustion (Black, McCance, and Young, 1944; Adolph, 1947).—Attributable purely to lack of drinking-water in a hot environment. Characterized in the earliest stage by thirst; vague discomfort, anorexia, impatience, weariness, sleepiness, dizziness; then tingling, dyspnoea, and cyanosis develop, and a walking pace cannot be maintained ("exhaustion" stage); eventually inability to stand, incoordination, restlessness, hysteria, or delirium ("collapse" stage). Potentially fatal, but may be relieved by water replacement.

Exercise-induced Heat Exhaustion.—Attributable to physical exertion (such as marching or digging) in a hot environment in the absence or deficiency of salt or water or sweating. Symptoms and signs are similar to those experienced after exertion in an ordinary environment, but relatively more severe. Exertion is usually stopped voluntarily at the stage of "exhaustion," or actual "collapse" may occur. Typical syncope may occur if the erect posture is assumed after a period of exertion (such as digging). Fairly rapid recovery after rest.

Heat Syncope.—Attributable to prolonged strain on the vasomotor system associated principally with the maintenance of the standing posture in a hot environment, and may be aggravated by psychological factors. Symptoms and signs are similar to those of syncope (fainting) in an ordinary environment. Rapid recovery after rest (Weiner, 1938).

Sunburn.—Attributable to exposure to sunlight. Acute erythema, familiar in temperate climates. If extensive may cause temporary malaise, headache, fever, and occasionally vomiting; in a hot climate may interfere with heat regulation, since affected areas lose vasomotor control and do not sweat.

Prickly Heat ("Miliaria Rubra").—Attributable to excessive sweating, particularly in hot, humid environments. Characterized by a fine, superficial, papular eruption, sometimes surmounted with vesicles, with some erythema of skin; usually accompanied by prickling (which may be present occasionally without eruption). Aggravated by heat stress (areas of skin usually kept covered most frequently affected). Often becomes infected and eczematized; subject to spontaneous regressions. Relieved by removal from heat stress. Healing frequently followed by anhidrosis, which may be extensive and lead to symptoms of heat intolerance.

Anhidrosis.—Generalized anhidrosis following prickly heat (usually with a characteristic appearance of the skin—"mammillaria," "miliaria profunda") may be observed in the absence of symptoms of heat intolerance. Exposure to heat stress will usually result in symptoms, however (anhidrotic heat exhaustion or collapse) (Horne and Mole, 1951).

Chronic Heat Neurotic Reaction: Chronic Heat Neurasthenia; "Tropical Neurasthenia"; "Tropical Fatigue" (Macpherson, 1949).—Attributable to prolonged exposure to a hot environment and particularly to its social and psychological implications; may or may not be accompanied by physical manifestations of the effects of heat or other organic disease. Characterized by deterioration, principally of characters and performance, but may also be physical. May simulate "effort syndrome." Symptoms usually long-standing—general mental and physical asthenia (loss of energy, initiative, interest); difficulty in concentrating, working, and sleeping; complaints of dizziness "blackouts"; loss of weight and appetite; irritability, bad temper, depression; fall in standard of performance; leading often to problems of conduct and discipline; may be aggravated by alcoholism and domestic and sexual problems. On examination little may be found. Sometimes unstable or neurotic personality. Important to eliminate "organic" effects of heat (such as salt or sweating deficiency) and physical disease. Symptoms usually relieved after removal from environment.

Mild Heat Fatigue: Mild Heat Asthenia; Acute Heat Neurasthenia (Stewart, 1945).—Attributable to short-term exposure to a hot environment, especially if badly ventilated (such as warship or factory) and if skilled or semi-skilled work is being undertaken; and in the absence of salt or water deficiency. Ill-defined symptoms of fatigue (not necessarily neurotic)—extreme tiredness, disinclination to work, irritability, errors in skilled performance. Symptoms rapidly relieved on removal of immediate stress. (This syndrome may be partly attributable to inadequate adaptation of the circulatory system, but evidence of this is commonly lacking, and the symptoms are predominantly "psychological.")

Heat Oedema.—Attributable to alterations in vasomotor (? circulatory) system during acclimatization to heat. Characterized by oedema of extremities, especially ankles; ranges from a feeling of tightness of footwear (or watch-strap) to incapacitating swelling of ankles and lower legs. Usually transient, clearing up on acclimatization or on relief from heat stress.

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"The problem of suicide requires special consideration in relation to the mental health of the aged. Suicide is now a major cause of death in all the economically advanced communities, and in the United Kingdom, where it is the cause of some 5,000 deaths yearly, this mortality now equals that due to pulmonary tuberculosis. In an ageing population, suicide and attempted suicide rates show a peak in senescence which usually occurs at a somewhat earlier age among women than men. . . . There is ample evidence that both social stress and psychiatric disorder are concerned in the growing problem of suicide among old people. Such factors do not, of course, operate in isolation. Social factors enhance the chances of becoming ill among those predisposed, while illness will often cause further decline in the social conditions of an old person, increasing his isolation and loneliness and forcing him often into an environment in which his hold on life proves to be tenuous and transient." From an address by PROFESSOR MARTIN ROTH on "Some Problems of Mental Health in Old Age," delivered at a meeting of the Royal Society of Health on June 17.

SURGICAL SHOCK

ANAESTHETISTS AT R.C.S.

[FROM A SPECIAL CORRESPONDENT]

On June 14 the Faculty of Anaesthetists held a whole-day meeting at the Royal College of Surgeons to discuss "Shock and Allied Phenomena."

Sir HENRY DALE, O.M., F.R.S., who opened the meeting, defined shock as any condition of depressed vitality with circulatory deficiency as its central feature but without evidence of haemorrhage or gross infection. Wound shock, he continued, might be due to absorption of toxic substances from the injured tissues. The analogy between wound shock and histamine shock was very close: in both the effective circulatory volume was greatly reduced, owing to stagnation of the blood and haemoconcentration from the leakage of plasma. He recalled some interesting experiments showing that histamine given intravenously to normal unanaesthetized cats did not produce shock, but when they were anaesthetized by chloroform, ether, or urethane the same dose of histamine produced shock. Moreover, he showed that it was not the state of anaesthesia itself but the sensitization effect of the anaesthetic agents which produced the shock-like state. Similarly, haemorrhage and adrenalectomy increased the sensitivity of the animals to histamine.

Causes of Irreversible Shock

Professor W. D. M. PATON, F.R.S., suggested that a number of causes could account for irreversible shock in dogs after haemorrhage. Thus "vasoexcitatory material" produced in response to haemorrhage would ordinarily be counteracted by "vasodilator material" from the liver, but if the latter's action were prolonged shock would ensue. Sluggish circulation coupled with an increased coagulability of the blood might lead to the formation of microemboli. Or, since clostridia were normally present in dogs' muscles, any hypoxia of the muscles would lead to elaboration of clostridial toxins. Finally, he suggested that vasoconstriction in itself could be the harmful factor in shock by producing tissue anoxia. A sluggish flow of blood through constricted arterioles into a progressively distending capillary bed would cause ischaemia, which in turn led to the release of potassium and histamine. This local release of histamine might not be accompanied by a detectable level in the peripheral blood. Other substances such as hydroxytryptamine and even the proteolytic systems of the body themselves acted on smooth muscle under these conditions. The toxic effects of adrenaline were well known. It blocked ganglia, and this effect lasted longer than its vasoconstrictor effect. Adrenaline could act, therefore, as a vasodilator and lymphagogue. In adrenaline shock, presumably the vasodilator effects completely overshadowed any vasoconstriction.

Experimentally, if the systolic pressure was maintained at about 40 mm. Hg by exsanguination, sympathetic amines were released, followed by histamine-like substances. If the blood volume was then restored, these histamine-like substances were washed into the general circulation in large quantities. They seemed to be released only so long as the spinal cord and its efferent pathways remained intact. The vasoconstrictor effect of defibrinated blood was due to hydroxytryptamine.

During shock the output of adrenaline continued, and therefore even in profound shock the vasomotor centre was still active. Vasoconstriction was essentially a damaging process, said Professor Paton: the periphery of the body was sacrificed to save the centre, but as a result of the sacrifice the centre died.

The Role of Ganglion-blockers

Dr. J. B. WYMAN then discussed the use of ganglion-blocking agents in major surgical procedures usually associated with severe shock. After haemorrhage there was a vicious cycle: venous return decreased, and this diminished cardiac output; blood pressure fell; vasoconstriction occurred, and this caused tissue hypoxia and increased capillary permeability; finally, the increase in permeability further reduced the effective circulatory volume. It was therefore the tissue perfusion rather than the blood pressure which was important. The ganglion-blocking agents were either adrenergic ones such as phenoxybenzamine or direct ganglionic blockers such as hexamethonium. Noradrenaline as a means of maintaining the blood pressure during these major interventions was clearly contraindicated, as it would increase tissue hypoxia; it would also encourage haemorrhage from the point of least resistance. Ganglion-blocking agents, on the other hand, protected the peripheral circulation, as shown by fluorescein studies, and phenoxybenzamine also prevented the release of "vasodilator material" by the liver. In animals the survival rate after haemorrhage was increased by giving ganglion-blocking agents, all the survivors showing haemodilution and the fatal cases haemoconcentration. Adrenaline assays showed also that the blood levels of adrenaline in the "blocked dogs" were much lower than in the controls.

Patients on Steroids

Dr. R. I. S. BAYLIS presented a very useful paper on the management of cases receiving cortisone and other steroids. The long-continued administration of drugs like hydrocortisone and prednisone led to a reduction in weight of the adrenal glands, which was accompanied by decreased pituitary corticotrophic activity due to pituitary inhibition. Corticotrophin exerted a similar effect on the pituitary by overstimulating the adrenal gland. After only seven days' prednisone therapy there was considerable adrenal depression in response to corticotrophin as measured by the output of urinary ketosteroids. The duration of this prednisone effect was at present unknown, but it probably lasted for a number of months. From the practical point of view, it was clearly vital for the surgeon to elicit any history of prednisone administration; equally patients should always be told if they were given prednisone.

Prophylactically, patients on steroids or who had had steroids during the previous 12 months should receive hydrocortisone, 100–200 mg. intramuscularly, 24 hours before operation, a similar dose two hours before operation, and 75–100 mg. after the operation. In addition they should be given 100 mg. daily by mouth for the next few days, and the dosage could then be reduced gradually over the next two weeks. If the patient was vomiting the drug could be given intramuscularly.

If shock occurred despite these measures, hydrocortisone hemisuccinate should be given intravenously (134 mg. is equivalent to 100 mg. of hydrocortisone); 400 mg. should be given in the first 24 hours, and, if there was no response to the intravenous administration of 100 mg. within 15 minutes, noradrenaline should be added in order to maintain the blood pressure until the steroid took effect.

Dr. A. J. W. BEARD presented a film on "Cardiac Arrest," stressing the importance of teamwork, speed rather than haste, and effective cardiac massage. Cardiac massage could be performed adequately only through a thoracotomy.

Estimation of Blood Loss

Mr. RUSCOE CLARKE, from the Birmingham Accident Hospital, maintained that wound shock was entirely due to haemorrhage. By ingenious limb measurements after trauma he showed that even in simple fractures of the femur as much as 3.5 litres of blood might be lost into the tissues. These results had been checked by blood-volume studies using ^{51}Cr and ^{32}P. He pointed out, moreover, that nobody had yet demonstrated a return of this "stagnant blood" into the circulation. It was important to remember that each bottle of blood contained only 400 ml. of blood, the remainder being citrate solution, and this might be important when large transfusions were given. Tissue-swelling after trauma occurred within an hour or so, and it must

be assumed to be due to extravasation of blood or plasma, with a corresponding diminution in the effective circulating volume.

Estimates of visible blood loss were always too low; but for practical purposes a fist was equivalent to a pint (570 ml.). In very extensive studies on blood volume, correlated with physical signs, he had found that, if the blood pressure was high and the pulse slow, then the effective blood volume was probably not below 80% of normal. In cases with a low blood pressure and a rapid pulse the blood volume might be reduced to below 50% and would certainly be below 60% of normal. However, the blood pressure and pulse were unreliable indices of blood volume. After transfusion, the blood pressure and pulse returned to normal before the blood volume was fully restored. Clinically, the toes became warm last of all and this was good evidence of a normal blood volume. An injured patient might lose 30 to 40% of his blood volume, and if surgery was contemplated this must be replaced, as a further loss of as little as one or two pints might prove critical: adequate pre-operative transfusion allowed adequate primary surgical treatment. In Mr. Ruscoe Clarke's opinion, noradrenaline at this stage was not indicated and the use of morphine and other drugs was entirely ancillary to transfusion.

The meeting ended with an account, by Dr. R. I. BODMAN, of the use of helicopters for the transport of patients.

BRITISH SOCIETY FOR IMMUNOLOGY

[FROM A SPECIAL CORRESPONDENT]

The great success of the British Society for Immunology, surprising even to its sponsors, is evidence that immunology has fully emerged from the temporary recession caused by the development of antibiotics. The spring meeting at the National Institute for Medical Research on June 13 and 14, attended by more than 250 people, began with a symposium on gamma-globulins, the protein fraction of the blood in which most humoral antibodies are found, and—as Dr. J. H. HUMPHREY (N.I.M.R.) pointed out in his introductory paper—the first molecules to have been used as "tracers" in biological research.

Nature of Humoral Antibodies

The theme of the first part of the symposium was the physical heterogeneity of the globulins. The alpha- and beta-globulins and the three components of gamma-globulin were defined by their electrophoretic mobility, said Dr. Humphrey, though this could be misleading: the immuno-electrophoretic definition might be nearer the truth. There was some evidence that not all gamma-globulins were in the strict sense antibodies: under antigenic stimulation the isolated perfused lung produced "non-combining" globulin as well as specific antibody. The antibodies produced by a single antigen might also be heterogeneous, different components being directed against different combining sites on the antigenic molecule.

Dr. R. R. PORTER (N.I.M.R.) said that the physical heterogeneity of antibodies was shown up by their particle sizes and solubilities quite independently of their electric charges; if to these three were added the serological variations of the antibodies directed against a single antigen, then antibodies could be said to be heterogeneous in four independent physical dimensions. These variations were not, however, reflected in their amino-acid composition. Some progress had been made with the partial proteolytic digestion of antibodies with papain: fragments with molecular weights of between 40,000 and 50,000 might retain their specific combining power. Still further evidence of heterogeneity was brought forward by Dr. A. S. MCFARLANE (N.I.M.R.). Labelled proteins belonging to a single molecular species were katabolized at a constant relative rate, whereas the rate of katabolism of gamma-globulins declined in the course of an experiment in the way that would be expected if they were heterogeneous. Correlation between the rates of formation of specific and non-specific globulin after antigenic stimulation by the intravenous and subcutaneous routes cast some doubt on the supposition that any high proportion of gamma-globulin was manufactured in peripheral lymphoid tissue.

Dr. P. BURTIN (Pasteur Institute, Paris) said that gamma-globulins, when used as antigens, had a similar immunochemical structure, but contained a number of different determinant groups. The gamma-globulins cross-reacted with the Bence Jones proteins found in the urine of patients with multiple myeloma, each such protein containing a few, usually one, of the determinant groups.

Hyper- and Hypo-gammaglobulinaemia

The discussion now turned to problems of more immediate clinical importance. Dr. N. H. MARTIN (St. George's Hospital), reviewing hypergammaglobulinaemia, limited his remarks to diseases such as chronic hepatitis, some collagen diseases, and some neoplasias, in which the circulating gamma-globulin levels were persistently greater than 1.6 g. per kg. body weight, so excluding the "healthy" transient increases that accompany other diseases. In chronic hepatitis the plasma cell count was proportional to the quantity of circulating gamma-globulin. Electrophoretic analysis of the serum in hepatitis suggested that the globulins present in excess extended over a wide range of mobility; over this range they were reactive to specific anti-gamma-globulin sera. As a corollary, modifying the normal gamma-globulins by simple chemical methods altered the electrophoretic behaviour without corresponding changes in specificity. Studies of globulins isolated from individual patients suffering from myelomatosis or having macroglobulinaemia showed clear-cut differences by physicochemical techniques, even though their globulins appeared to retain areas of common immunological pattern. He suggested that the differences might be of secondary structure rather than of primary amino-acid sequence.

Professor J. R. SQUIRE (Birmingham University) defined hypogammaglobulinaemia in terms of a gamma-globulin level less than 200 mg. per 100 ml. plasma, subject to there being an otherwise normal electrophoretic pattern and no protein in the urine. In such patients antibodies were generally absent even after active immunization. Hypogammaglobulinaemia was a low-production syndrome and was not due to an abnormally high rate of elimination, since normal gamma-globulins injected as replacement therapy showed a normal rate of decay in the circulation. He suggested that lack of a plasma cell maturation factor might be the cause of hypogammaglobulinaemia, for large numbers of plasma cell precursors were found in the liver. Most patients also lacked two of the beta components of serum globulins and the ABO iso-agglutinins, but where spontaneous recovery occurred, as it did in 20% of cases, the beta-2m factor was always present. In eight of the forty known British cases, tuberculin sensitivity and drug allergy were demonstrable, indicating that hypersensitivity reactions were unaffected by the gamma-globulin deficiencies.

Dr. R. G. WHITE (London Hospital) described work on the cells concerned with the synthesis of gamma-globulins and antibodies. By the fluorescent-antibody technique he showed localization of antibody in the nucleus and cytoplasm of plasma cells, and these cells were histologically similar to other cells secreting proteins. By preparing fluorescent antibodies to gamma-globulins in other species he demonstrated the accumulation of gamma-globulin in the cytoplasm of some plasma cells. Immature cells showed the greatest antibody content, and the appearance of Russell's bodies might mark the end of the antibody-forming response. It appeared from this and other evidence that individual plasma cells responded to a single antigenic

stimulus. By using the fluorescent-antibody technique Dr. White demonstrated beautifully that a lymph node stimulated by two distinct antigens had two distinct populations of cells.

Selected Papers

A selection only of the papers presented at the general meeting is here reported. A paper given by Dr. SYLVIA LAWLER (University College, London) described the classification of human sera into two groups, by their inhibitory or non-inhibitory action on sensitized red blood cells in the presence of rheumatoid arthritic sera. This system was of serological interest and had already been used in population studies. Frequencies already determined were 60% inhibitors in Britain and Sweden, 40% in Italy, and 90% in Eskimo populations.

Dr. L. BRENT, Miss JEAN BROWN, and Professor P. B. MEDAWAR, F.R.S. (University College, London), showed that a hypersensitivity reaction of the delayed type was associated with the breakdown of skin homografts in guinea-pigs. This reaction was transferable with sensitized cells, giving further evidence of the important part played by cell-bound antibodies in such reactions.

The Rous sarcoma agent does not normally "take" in turkeys, but can be made to do so if the turkeys are injected with chicken's blood immediately after hatching. Drs. R. J. C. HARRIS and P. J. SIMONS (Chester Beatty Research Institute) reported that the antigen conferring tolerance is present in guinea-pig's blood, hog gastric mucin, and human corpuscles of group A; there was little doubt that it was blood-group A substance itself.

Earliest Age for Polio Vaccination

Dr. F. T. PERKINS (M.R.C. Laboratories, Hampstead) reported work on the serological response of young babies to poliomyelitis vaccine. He had divided 88 babies into three groups and studied the antibody levels in their serum before and after injection of vaccine at 1, 6, and 10 weeks. While the maternal level of antibody was high in the circulation, a poor response was obtained; the general level of response was much lower than that obtained in the age-group 1–10 years. Early injection of the vaccine did not result in a heightened response to secondary injections. Dr. Perkins considered that the earliest age at which a good enough response is obtained to justify vaccination would be six months.

Qualitative and quantitative correlations were demonstrated by Drs. I. MOTA and J. H. HUMPHREY (N.I.M.R.) between the occurrence of anaphylaxis and the degranulation of mast cells in the guinea-pig; mast-cell damage alone was sufficient to cause death. In the rat two types of mast-cell damage occurred: one, after active immunization by the intraperitoneal route, which disrupted the cell granules and released histamine into the circulation; the other reaction occurred after passive sensitization, or active sensitization by the subcutaneous route, and was not accompanied by histamine release. Damage to cells other than mast cells must therefore be important in the anaphylactic mechanism in the rat.

Hashimoto's Thyroiditis

Drs. I. M. ROITT and DEBORAH DONIACH (Middlesex Hospital) had continued their investigation of Hashimoto's thyroiditis as a disease caused by auto-immunization. Two kinds of humoral antibody had been detected: a precipitin which could be titrated as an agglutinin by the tanned red cell technique, and a complement-fixing antibody, probably directed against a microsomal antigen, which might not be peculiar to thyrotoxicosis. There were reasons for believing that the antibody responsible for cellular destruction in Hashimoto's disease was cellular rather than humoral; they recalled Dr. Witebsky's evidence that induced autoimmune thyroiditis in rabbits could not be transferred passively with immune serum.

Nova et Vetera

CENTENARY OF THE DARWIN–WALLACE PAPER ON NATURAL SELECTION

The occasion on which the doctrine of Evolution by means of Natural Selection was first presented to the world is worthy of its own centenary celebrations. Its scientific importance will be reviewed and evaluated at an international meeting arranged in its honour (the XVth International Congress of Zoology, London, July 16–23), but there are other aspects of the occasion which are both interesting and instructive. The circumstances leading to the publication of the celebrated Darwin–Wallace paper have been recorded in considerable detail by those most closely concerned in them, and they are worth recalling for the great light which they shed on four great scientific figures of Victorian England.

The turning-point in the life of Charles Darwin was his five-year voyage in the *Beagle*. When he left England in December, 1831, he was a young man intending to enter the Church and devote his leisure to geology, having abandoned medicine after two years at Edinburgh, when he learned that he would never need to earn his own living. He was vigorous, gay, sociable, excessively fond of shooting game-birds, and already an assiduous collector and recorder. He had read the *Zoonomia* of his famous grandfather, Erasmus, in which evolutionary theories of a kind are discussed, and had deplored the dearth of facts and the excess of speculation in that work. The journal of his voyage (which has won its place as a classic of scientific literature) reveals how deliberately he set out to collect the necessary facts. His letters home, to Professor Henslow, his Cambridge

Charles Darwin at age of 51.

Alfred Russel Wallace.

Sir Charles Lyell.

Sir Joseph Dalton Hooker.

patron and friend, and to others, were full of new information and won him a reputation as a discerning naturalist even before his return. As early as July, 1837, on completing the transcript of his journal for publication, he was convinced that evolution was the only possible interpretation of the evidence. In October, 1838, he tells us in his autobiography :

"I happened to read for amusement Malthus on *Population*, and being well prepared to appreciate the struggle for existence which everywhere goes on from long-continued observation of the habits of animals and plants, it at once struck me that under these circumstances favourable variations would tend to be preserved, and unfavourable ones to be destroyed. The result of this would be the formation of new species. Here, then, I had at last got a theory by which to work; but I was so anxious to avoid prejudice, that I determined not for some time to write even the briefest sketch of it. In June, 1842, I first allowed myself the satisfaction of writing a very brief abstract of my theory in pencil in 35 pages; and this was enlarged during the summer of 1844 into one of 230 pages, which I had fairly copied out and still possess."[1]

Meantime, having lived for two years in bachelor apartments in Great Marlborough Street, when he acted as one of the honorary secretaries of the Geological Society, he had married in January, 1839, and set up house at 12, Upper Gower Street, but he blamed life in London for a breakdown in health, and in July, 1842, a month after writing out his first "abstract," moved to Downe House, near Farnborough, in Kent. There, having settled down to a quiet domestic routine, he continued to collect materials and make notes for the great work which he would publish "one day." And there, but for the stimulus provided by a challenge from the other side of the world, and but for the loyalty and energy of two of his best friends, he might have spent the remainder of his days collecting and note-taking, unknown to the great world save as the author of the splendid *Journal*. It is a situation not unfamiliar in scientific circles.

Charles Lyell and J. D. Hooker

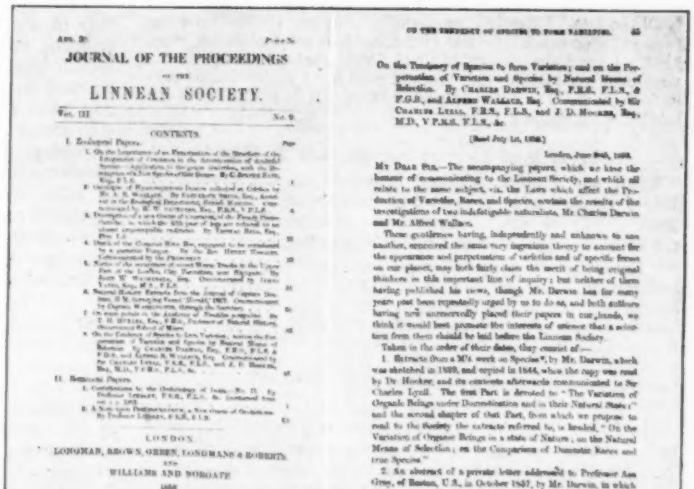
The two friends were Charles Lyell (1797–1875), the celebrated author of the *Principles of Geology* (1830–3), and Joseph Dalton Hooker (1817–1911), the botanist and traveller. Darwin tells us : "I saw more of Lyell than of any other man both before and after my marriage. His mind was characterized, it appeared to me, by clearness, caution, sound judgment and a good deal of originality. . . . A second characteristic was his hearty sympathy with the work of other scientific men."[2] Hooker had first come to know of Darwin by reading the proofs of his *Journal* when he was in his final year of medical studies at Glasgow University. After returning from the Antarctic, where he served as naturalist to the Ross expedition, he wrote to Darwin and so began a lifelong friendship between the two men. Darwin found him "a delightfully pleasant companion and most kind-hearted. One can see at once that he is honourable to the backbone. His intellect is very acute."[3] His father, Sir William Hooker, was Director of Kew Gardens, a post to which he himself succeeded in 1865.

The challenge came from a young man who was earning his living by collecting specimens of plant and animal life in the Malay Peninsula. Fourteen years Darwin's junior, he had been fired with determination to visit the tropics as a collector by reading Darwin's *Journal* at the age of 19. In 1856 Lyell drew Darwin's attention to a paper in the *Annals and Magazine of Natural History* of 1855, of which this same young man, Alfred Russel Wallace, was the author.[4] Its title was "On the Law which has Regulated the Introduction of New Species," and it contained views similar to those on which Darwin was himself working. Lyell advised Darwin to write a preliminary sketch for publication. Impressed by Lyell's urging, but disliking the idea of "writing for priority," Darwin began, with his usual thoroughness, to do so "on a scale three or four times as extensive as that which was afterwards followed in [the] *Origin of Species*, yet it was only an abstract. . . ." While he was immersed in this task a letter from Wallace, written at Celebes on October 10, 1856, reached him at Downe in the last week of April, 1857. This letter was further proof of their identity of view, and Darwin replied sympathetically, if cautiously, taking care to point out that he had been collecting the data necessary to prove this theory for nearly 20 years. In answer to another letter received in the following December he wrote to Wallace, "I believe I go much further than you; but it is too long a subject to enter on my speculative notions."

Wallace's Essay

Work continued on "the big book." In the spring he went for one of his customary sojourns in a hydropathic establishment at Moor Park, near Farnham, and about a month after his return, on June 18, 1858, he received from Wallace in the Island of Ternate, in the Moluccas, a manuscript essay entitled "On the Tendency of Varieties to depart indefinitely from the Original Type." The writer asked Darwin, if his own opinon was favourable, to send it to Lyell, presumably with a view to publication. We do not have to guess at Darwin's feelings on reading this essay; they are plain in the letter with which he forwarded the essay to Lyell on that same day.

"Your words have come true with a vengeance—that I should be forestalled. You said this, when I explained to you here very briefly my views of 'Natural Selection' depending on the struggle for existence. I never saw a more striking coincidence; if Wallace had my MS. sketch written out in 1842, he could not have made a better short abstract! Even his terms now stand as heads of my chapters. Please return me the MS., which he does not say he wishes me to publish, but I shall, of course, at once write and offer to send to any journal. So all my originality, whatever it may amount to, will be smashed, though my book, if it will ever have any value, will not be deteriorated; as all the labour consists in the application of the theory. . . ."[5]



JOURNAL OF THE PROCEEDINGS
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Vol. III No. 9.

CONTENTS.

LONDON:
LONGMAN, BROWN, GREEN, LONGMANS & ROBERTS.
AND
WILLIAMS AND NORGATE.
1858.

ON THE TENDENCY OF SPECIES TO FORM VARIETIES. 45

On the Tendency of Species to form Varieties; and on the Perpetuation of Varieties and Species by Natural Means of Selection. By CHARLES DARWIN, Esq., F.R.S., F.L.S., & F.G.S., and ALFRED WALLACE, Esq. Communicated by Sir CHARLES LYELL, F.R.S., F.L.S., and J. D. HOOKER, Esq., M.D., V.P.R.S., F.L.S., &c.

[Read July 1st, 1858.]

The first cover of the original issue of the *Journal of the Proceedings of the Linnean Society* containing the Darwin–Wallace communications. (From the copy in the Wellcome Historical Medical Library.)

The first page of the Darwin–Wallace communications, with the introductory letter (ending on page 46) signed by Lyell and Hooker.

After a week's pondering on his course of action, he wrote again to Lyell :

My dear Lyell,—I am very sorry to trouble you, busy as you are, in so merely personal an affair; but if you will give me your deliberate opinion, you will do me as great a service as ever man did, for I have entire confidence in your judgment and honour. . . .

There is nothing in Wallace's sketch which is not written out much fuller in my sketch, copied out in 1844, and read by Hooker some dozen years ago. About a year ago I sent a short sketch, of which I have a copy, of my views . . . to Asa Gray, so that I could most truly say and prove that I take nothing from Wallace. I should be extremely glad now to publish a sketch of my general views in about a dozen pages or so; but I cannot persuade myself that I can do so honourably. . . . I would far rather burn my whole book, than that he or any other man should think that I had behaved in a paltry spirit. Do you not think his having sent me this sketch ties my hands? . . . This was my first impression, and I should have certainly acted on it had it not been for your letter.

This is a trumpery affair to trouble you with, but you cannot tell how much obliged I should be for your advice.

By the way, would you object to send this and your answer to Hooker to be forwarded to me, for then I shall have the opinion of my two best and kindest friends. This letter is miserably written, and I write it now, that I may for a time banish the whole subject; and I am worn out with musing. . . . My good dear friend, forgive me. This is a trumpery letter, influenced by trumpery feelings.

Yours most truly,

C. Darwin.

I will never trouble you or Hooker on the subject again.[6]

On the following day he sent yet another note to Lyell "adding a P.S. to make the case as strong as possible against myself," but before the reply reached him yet another blow fell. There was an outbreak of scarlet fever at Downe, and the death of his youngest child, Robert Waring, at the age of 2, brought grief to the whole Darwin family. His daughter Henrietta was ill, the two nurses brought in to look after the children also fell ill, and all the children had to be moved away. On the morning of Tuesday, June 29, Darwin wrote to Hooker: ". . . I have received your letters. I cannot think now but soon will."[7] And that same night he wrote again :

"I have just read your letter, and see you want the papers at once. I am quite prostrated, and can do nothing, but I send Wallace, and the abstract of my letter to Asa Gray, which gives most imperfectly only the means of change, and does not touch on reasons for believing that species do change. I dare say it is all too late. I hardly care about it. But you are too generous to sacrifice so much time and kindness. It is most generous, most kind. I send my sketch of 1844 solely that you may see by your own handwriting that you did read it. I really cannot bear to look at it. Do not waste much time. It is miserable in me to care at all about priority. . . ."[8]

Meeting of Linnean Society, July 1, 1858

Lyell and Hooker worked fast, and on the evening of July 1 the Darwin–Wallace paper was read at the Linnean Society. There was no discussion. Hooker later described the evening in a letter to Charles's son, Francis:

"The interest excited was intense, but the subject was too novel and too ominous for the old school to enter the lists before armouring. After the meeting it was talked over with bated breath: Lyell's approval, and perhaps in a small way mine, as his lieutenant in the affair, rather overawed the Fellows, who would otherwise have flown out against the doctrine. We had, too, the vantage ground of being familiar with the authors and their theme."[9]

On July 5 Darwin wrote to Hooker to express his gratitude. "You must know," he wrote, "that I look at it, as very important, for the reception of the view of species not being immutable, the fact of the greatest Geologist and Botanist in England taking *any sort of interest* in the subject: I am sure it will do much to break down prejudices."[10]

Wallace too was grateful for the course taken by Lyell and Hooker, and the letter which arrived at Downe in the following January convinced Darwin "how generous and noble was his disposition," and led to a lifelong friendship based on mutual confidence and respect.

The joint paper was published in the *Journal of the Proceedings of the Linnean Society* dated August 20, 1858 (Vol. III, No. 9). Its reception and influence, together with that of the "brief abstract" which was published with the title *On the Origin of Species by means of Natural Selection* on November 24, 1859, has been the subject of many books and papers. That the paper alone was sufficient to convert one distinguished naturalist, and he a churchman, is clear from the publication, in October, 1859, of Canon Tristram's paper "On the Ornithology of Northern Africa."[11] The impression which it made on the younger men may be judged by the reaction of Alfred Newton, professor of comparative anatomy at Cambridge from 1866 to 1907. He read it soon after his return from Iceland in 1858 and to him "it came like a direct revelation of a higher power."[12] Nearly 30 years later Professor Newton, in an address to the British Association, drew a moral from the circumstances of its publication:

"If in future you should meet with any cynic who may point the finger of scorn at the petty quarrels in which naturalists at times engage, particularly in regard to the priority of their discoveries, you can always refer him to this greatest of all cases, where scientific rivalry not only did not interfere with, but even strengthened, the good-feeling which existed between two of the most original investigators."[13]

He could also have added that the conduct of Lyell and Hooker, who, through the years when they were offering sympathy and encouragement to Darwin, and even after the presentation of the Darwin–Wallace paper, remained unconvinced by Darwin's arguments, provide a splendid example of scientific integrity and of that respect for freedom of thought and speech which were the mainspring of progress in the nineteenth century.

F. N. L. POYNTER.

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10 —— *op. cit.*, Vol. II, p. 127.
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"The most considerable edifice [in Lincoln's Inn Fields] is that of the College of Surgeons, and contains a very interesting museum. One of the gentlemen showed me the establishment with great civility. The first thing that claimed my attention was a very pretty little mermaid which had been exhibited here for money some years ago, and was afterwards sold for a thousand pounds, when it was discovered that she was a deceptive contrivance made out of a small ourang-outang and a salmon, joined together in a most workmanlike manner. The existence of such creatures remains, therefore, as much a problem as ever. Near to it stood a real large ourang-outang, who lived here for a long time and performed many domestic services in the house. Mr. C. (so my informant was called) assured me that he must regard this animal as a distinct genus, nearer to man than to the ape. He had long and attentively observed this individual, and had found in him the most certain proofs of reflection and combination, evidently far beyond the reach of instinct. Then he remarked that Mr. Dick, as he called him, felt in gentlemen's pockets, if he were permitted, for eatables; but if his search was unsuccessful, carefully replaced everything that did not answer his purpose, instead of throwing it away or letting it fall as other monkeys do. He was so sensitive to the slightest mark of displeasure that he was depressed and unhappy for days after being unkindly spoken to. He was observed, too, to try of his own accord to assist the servants, if he saw them unusually oppressed with work."—From *A Regency Visitor* (The English Tour of Prince Pückler-Muskau, Described in his Letters, 1826–1828). Collins, 1957, London.

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Scheriproct Ointment (Pharmethicals (London) Ltd.).—This contains prednisolone 0.15%, dibucaine chlorhydrate 0.5%, hexachlorophene 0.5%, and menthol 0.2%.

The local application of hydrocortisone or prednisolone is no doubt a most valuable treatment for pruritus ani. Combined with an antiseptic it is of value in some cases of psoriasis and seborrhoeic dermatitis affecting the perineum.

Its effect in relieving irritation presumably derives from its anti-inflammatory property, so that the relief of irritation is not secured at once. No doubt this is the reason why dibucaine and menthol are included in this prescription. As a rule, however, dermatologists are rather opposed to the local application of these anaesthetics to the skin because of the risk of producing epidermal sensitivity and consequent dermatitis. It may be thought that the presence of prednisolone will obviate that risk, but this is doubtful. The ointment may therefore be expected to be effective for the conditions for which it is intended, but the physician should keep constantly in mind the possibility of epidermal sensitivity arising.

N.H.S. basic price: 10 g. tube, 9s. 6½d.

Lipostabil Capsules (John Ronaldson & Co. Ltd.).—This preparation contains 175 mg. of soya bean lecithins, 100 mg. of a "tween"-like compound (3-4-5 polyoxyethylene-sorbitol mono-oleate), potassium theophyllinate 50 mg., and potassium thiocyanate 50 mg. It is claimed that these capsules produce and maintain a normal cholesterol–phospholipid ratio, and that they are indicated for prophylaxis of atherosclerosis and coronary occlusion and to retard the atherosclerotic process when already present.

It has not been established which of these somewhat heterogeneous components is the most effective, and sufficient studies have not yet been made to substantiate the claim that this preparation will maintain a normal cholesterol–phospholipid ratio for any length of time. At present there is no evidence from investigations in man that production of a normal cholesterol–phospholipid ratio offers any prophylaxis against atherosclerosis or retards existing atherosclerosis. The claims for this preparation are based on theoretical possibilities and more extensive investigation is required before its prescription can be advocated.

N.H.S. basic price: 100 capsules, 14s. 5d.

Asmapax Ionexten-Tabs (Clinical Products Ltd.).—One tablet contains equivalent of ephedrine gr. ¼ (50 mg.) in resin-bonded form, theophylline 65 mg., bromvaletone 150 mg., and mephenesin 50 mg.

Asmapax is a proprietary tablet for the relief of bronchospasm. The ephedrine is in resin-bonded form with the object of securing slow release and absorption; this may minimize the unwanted effects such as wakefulness and palpitations, and prolong the total duration of action. The theophylline has a mild activity in relaxing bronchospasm, but also would tend to increase wakefulness. Bromvaletone is included presumably for its sedative action, counteracting the unwanted stimulant effects of ephedrine and theophylline. Mephenesin relaxes striated muscle by a central action and has a mild sedative effect, which has been claimed to be of some value in anxiety states. Presumably only the latter action can be intended in a preparation for use in asthma, but it seems doubtful whether any effect would be produced by the minute dose included in this preparation. The preparation may be regarded as yet another addition to the many combinations of antispasmodic and sedative drugs intended for the symptomatic treatment of asthma.

N.H.S. basic price: 30 tabs., 5s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Undescended Testicles

SIR,—The term undescended testicles, as used at the present time, includes two quite distinct groups; normal variations of development, in which hormone treatment is unnecessary, and congenital deformities, in which it is useless. There are few things which children dislike more than a series of injections, and, in the hope of diminishing the amount of needless suffering caused by this treatment, I outline under seven headings the objections to it from the point of view of a paediatric surgeon.

Logical.—The treatment is founded on work done on rats, in which hormones accelerate a normal process which would have occurred in any event. It is difficult to make out whether endocrinologists claim to do more in humans.

Statistical.—The diagnosis of undescended testicles is four times as frequent in schoolboys as in adults, both groups being untreated. This means that three-quarters of the supposedly misplaced organs take up the usual adult position spontaneusly, in other words are normal variations. If the successes of hormone treatment do not come from this group, where do they come from?

Mechanical.—The commonest type of testicle to be labelled "undescended" is the "low retractile," in which the cord is long enough to allow the testicle to reach the bottom of the scrotum but its lightness and the high tone of the cremaster hold it in the superficial inguinal pouch. The effect of hormones is not to lengthen the cord but to produce swelling and increase of weight, with consequent overcoming of muscular resistance to descent.

Physiological.—I am willing to accept that if hormones are not given in dangerous doses there is no danger. But anyone working on this subject knows that safety limits are frequently exceeded, particularly in treating the congenital deformity group. In the early accounts of enthusiasts, and in all commercial advertisements I have seen, there is no mention of dangers.

Psychological.—I have mentioned the fear that many boys have of a series of injections at set intervals. Psychological disturbances as a result of premature stimulation of the sex instinct have been described, and I have had complaints of this kind from parents. I suppose it is necessary in the interests of science to set young men worrying about their sperm counts, but I suggest this line of investigation should be kept to a minimum for obvious reasons.

Diagnostic.—My experience is that hormones are quite unreliable as a means of diagnosis. I have known small retractile testicles remain exactly the same in spite of a long series of injections; and the same lack of effect in the only diagnostically difficult cases, where the classification lies between high retractile and inguinal ectopic. I find that palpation and a knowledge of anatomy will enable three-quarters of the considerable number of cases sent up to me for an opinion to be sorted out as normal, and consider these are probably those which supply the difference between the frequencies of "undescended testicles" in children and in adults.

Anatomical.—The first essential in treating any anatomical condition is to learn the anatomy. Endocrinologists still appear to believe that they can feel testicles in the inguinal canal, and bring them out of it into the scrotum: actually these testicles which can be felt above the pubis have emerged from the canal and are lying superficial to it. A testicle in the canal lies in a hernial sac (which needs operation anyway) and cannot be felt. Anyone who doubts this should examine carefully, both before and during operation, the variety I have described as "emergent." In this the testicle emerges from the canal and can be felt easily while the boy is active; but when he is relaxed, particularly under anaesthesia, it slips back into its hernial sac, which opens freely into the peritoneal cavity, and cannot be felt through the external oblique. This is the variety which puts surgeons wrong: it illustrates the fact that a testicle cannot be described as having a position, but only as having a range of movement: in this case a hair-pin shaped course down the canal and then back over the same track in the superficial inguinal pouch. In fat boys a report is common that no testicles at all can be felt, though the experi-

enced find small retractile ones without undue difficulty; hence my disbelief of accounts of bringing testicles out of the abdominal cavity.

Drs. J. Brunet, R. R. de Mowbray, and P. M. F. Bishop in their paper on the management of the undescended testis (*Journal*, June 14, p. 1367) use the terms "retractile testicles" and "superficial inguinal pouch," but neither define them nor give any reference to the paper in which they were first defined.[1] The statements in this paper are either incorrect or else they destroy the whole basis of hormone treatment. Perhaps some day the anatomists will investigate them, and if they are found accurate, rewrite their accounts of the region.—I am, etc.,

London, W.1. DENIS BROWNE.

REFERENCE

[1] Browne, Denis, *Brit. med. J.*, 1938, **2**, 168.

Treatment of Parkinsonism

SIR,—I have read the article written by Drs. William Hughes, Janet H. Keevil, and Irene E. Gibbs (*Journal*, April 19, p. 928) giving their results of a trial with a new remedy—Ciba 10870 or 3-phenyl-3(β-diethyl-aminoethyl)-2,6-dioxopiperidine hydrochloride. The method they use was not satisfactory for the following reasons:

The total number of patients treated was only 16 and these are insufficient to prevent the favourable results represented being due to pure chance. Furthermore, this figure was further diluted by three patients being rejected from the trial due to symptoms from the withdrawal therapy.

The investigators' clinical judgment is not put to the test as recommended by Gillhespy and Ratcliffe.[1] Their statement that "the general impression was that the new preparation was equal if not superior to any therapy in current use" is simply not true, as none of the patients included in this trial was receiving "disipal" (β-dimethylaminoethyl-2-methylbenzhydryl hydrochloride) or "pacatal" (10-(1-methyl-3-piperidylmethyl)-phenothiazine), and only one was receiving "lysivane" (ethopropazine hydrochloride).

Drug or Combination of Drugs	No. of Patients Receiving Drug
"Disipal" (β-dimethylaminoethyl-2-methylbenzhydryl hydrochloride)	86
"Lysivane" (ethopropazine hydrochloride)	53
"Pacatal" (10-(1-methyl-3-piperidylmethyl)-phenothiazine)	34
"Artane" (benzhexol hydrochloride)	20
"Cogentin" (benztropine methanesulphinate)	17
"Disipal"+"lysivane"	46
"Hyoscine spansule capsules"+"hystryl spansule capsules"	28
"Disipal"+"pacatal"	10
"Lysivane"+"artane"	7
"Pacatal"+"oblivon C" (methylpentynol carbamate)	5
"Disipal"+"artane"	5
"Disipal"+"thephorin" (pheninamine tartrate)	5
"Lysivane"+"oblivon C"	3
"Pacatal"+"lysivane"	3
"Disipal"+"oblivon C"	3
"Artane"+"pacatal"	2
"Lysivane"+"thephorin"	1
Trial mixture (procyclidine hydrochloride, methedrine hydrochloride, hyoscine hydrobromide)	18
"Disipal"+"lysivane"+"artane"	16
"Lysivane"+"artane"+"thephorin"	9
"Lysivane"+"artane"+"pacatal"	9
"Disipal"+"lysivane"+"thephorin"	8
"Hyoscine spansule capsules"+"histryl spansule capsules"+"disipal"	7
"Lysivane"+"disipal"+"oblivon C"	2
"Lysivane"+"pacatal"+"oblivon C"	1
Total patients attending regularly	398

None of the patients were receiving the most efficient combinations of disipal+lysivane. That these are the most efficient drugs in current use for the treatment of Parkinsonism is proved by a recent survey of 398 patients attending my Parkinson's clinic regularly. The numbers found to be taking each drug or combination of drugs are shown in the Table. Furthermore, these drugs, except when given in high dosage, do not have dangerous side-effects, but mild unpleasant effects occur more frequently but can usually be controlled by modification of the dose.—I am, etc.,

Birmingham, 18. R. O. GILLHESPY.

REFERENCE

[1] Gillhespy, R. O., and Ratcliffe, A. H., *Brit. med. J.*, 1955, **2**, 352.

SIR,—We have read with interest the article by Drs. William Hughes, Janet H. Keevil, and Irene E. Gibbs (*Journal*, April 19, p. 928) on the use of Ciba 10870 (3-phenyl-3(β-diethyl-aminoethyl)-2,6-dioxopiperidine hydrochloride) in the treatment of Parkinsonism, and should welcome an opportunity to comment briefly on our own experience in this connexion.

We have, so far, treated 19 patients with post-encephalitic Parkinsonism and four with paralysis agitans. They received Ciba 10870 by mouth, in divided doses, to a daily total of 22.5–30 mg. of a "triplex" (slowly absorbed) form of 10870, or 7.5–10 mg. as ordinary tablets. The treatment periods ranged from 10 to 15 days. All these patients had previously been under regular treatment with the other anti-Parkinsonian remedies, chiefly benzhexol and scopolamine, which clinical trial had shown to suit them best. In order to avoid the complicating factor of a sudden change of therapy the Ciba 10870 was only gradually substituted for the previous regime. Then, at the end of the trial period, an overall rating of the value of the drug was made on the basis of the patients' subjective impressions and of the objective observations made by the medical staff and by the nurses.

The results (see Table) show that in the higher dosage of 22.5–30 mg. per day Ciba 10870 caused further improvement, as compared with the previous best therapy available, in about half the patients. The results with a dose of 7.5–10 mg. were not so impressive, and this amount is clearly insufficient. The beneficial effect of Ciba 10870 was greatest on muscular rigidity, but it was our impression that tremor was also improved, and that in two patients the frequency and intensity of oculogyric crises (a notoriously intractable symptom) were reduced. In 10–80% of patients the therapy with the higher dosage of Ciba 10870 was very well tolerated. The most frequent side-effects were dryness and burning in the mouth and epigastrium. Other side-effects, observed only rarely, included nausea and vomiting, mydriasis, and hypotension. These symptoms were, however, never severe enough to necessitate withdrawal of the drug.

Dose (mg./day)	No. of Observations	Therapeutic Effect			Incidence of Side-effects (%)
		Improved	No Change	Worse	
22·5–30	25	11	11	3	20
7·5–10	10	1	7	2	30

Our preliminary results agree closely with those of Dr. Hughes and his colleagues, and suggest that a more extended trial of Ciba 10870 for the treatment of Parkinsonism is well merited.—We are, etc.,

Padua, Italy. ANTONIO BALESTRIERI. UMBERTO SIGNORATO.

Tuberculosis in Dairy Workers

SIR,—A recent report from Switzerland[1] describes the occurrence of tuberculosis among cattle in a dairy herd which had been free from bovine tuberculosis for several years. The infection was found to be of the human type and there was some evidence of infection among members of a farm worker's family who had been in contact with the animals. The problem of reinfection of dairy cattle from non-bovine sources is also discussed by Hofmann,[2] who reported that 80% of the dairy herds in Switzerland were free from tuberculosis in 1956 and that it was hoped to eradicate the disease entirely from Swiss dairy herds by the end of 1958.

As you are no doubt aware, good progress is also being made in the Area Eradication Plan for bovine tuberculosis in this country, and at the end of 1956 about 67% of all cattle in this country were in attested areas. With the disappearance of bovine tuberculosis from dairy herds in this country the possibilities of reinfection of dairy cows from human sources must obviously not be overlooked, and it might in the long run be advisable to keep a special check on the health of farm personnel in contact with dairy cattle.—I am, etc.,

Shinfield, near Reading. E. J. MANN,
Director,
Commonwealth Bureau of Dairy Science and Technology.

REFERENCES

[1] Kuslys, A., *Schweiz. Arch. Tierheilk.*, 1958, **100**, 278.
[2] Hofmann, W., ibid., 1956, **98**, 545.

Imbecile Children

SIR,—Nobody will deny that mongol and other imbecile children do far better if they are well cared for at home by devoted and affectionate parents. But the parents of these children are always haunted by anxiety about the child's future when they are no longer able to provide the necessary care and shelter. Furthermore, the parents are often appalled by the prospect of having an imbecile child perpetually on their hands, and of being unable ever to leave the child with someone else while they take a much-needed holiday. If the parents of normal children sometimes feel the need of a break from their children's company, how much greater is the need of an occasional respite for the parents of an imbecile child.

There is the further problem of the effect of an imbecile sibling on his brothers and sisters. During the early years the imbecile child will be well tolerated and made much of as a family pet, but with the passage of time the difficulties of the brothers and sisters in coping with the abnormal child increase and eventually the situation in the family becomes intolerable. On the other hand, if such a child is "put away" at once in an institution—and this is usually well-nigh impossible owing to long waiting-lists—the child suffers and the parents carry with them through life a sense of guilt at having turned their back on their unfortunate offspring.

To overcome the difficulties stated above I would like to see every imbecile child affiliated as soon after diagnosis as possible to a mental hospital. This should preferably be the one nearest his home. The child would at first be brought for visits as an out-patient. These visits would develop into play sessions to enable the child to get to know the place and to make friends among the staff and the other patients. An occasional social function in the form of a party would also be an advantage. The mental hospital should be able to provide facilities for the temporary admission of a child while the parents take a holiday. Such facilities do in fact exist to a limited extent at the Fountain Hospital, Tooting, and are greatly appreciated by the parents. Eventually the child, now no longer so vulnerable to removal from home and having grown accustomed to the mental hospital and regarding it as a home-from-home, could, if the need arose, be admitted permanently without psychological injury.

The benefits of such a scheme would be great. The child would be weaned gradually from parental care and the parents would be able to see an eventual end to their great ordeal; an end which would be achieved without the need for a searching of the conscience and a lasting sense of guilt. It is my belief that if the parents of an imbecile child knew that such arrangements existed the majority of them would gladly keep their children at home during the important early years and the result would be a considerable lessening of the demand for places in institutions which exist for the care of imbecile children.—I am, etc.,

London, S.E.26. JOHN BURKINSHAW.

Social Problems of Prematurity

SIR,—Referring to a recent paper[1] of mine, in a leading article entitled "Social Problems of Prematurity" (*Journal*, June 7, p. 1343), your leader writer states that my observation of a relationship between prematurity rate and mother's childhood environment is difficult to interpret. It is not clear whether he accepts the finding but is not sure about its medical and social bearing, or whether this is a polite way of saying that he does not believe it. Let me first assure him that the correlation between prematurity rate and the social class of the mother's father was observed consistently from the start of inquiry, that it was a most unexpected finding, and that it is highly significant. He objects that the mothers might have stated their father's occupation incorrectly. If so, this would tend to mask a real correlation, and could not produce one as an artifact. He does not mention that a check was provided by the independent interview of more than one hundred grandmothers in their own homes. This section of the paper is probably the most valuable, as it provided a striking confirmation of what, until then, had been a supposition.

He further objects that the Registrar-General's occupational classification is only a very rough measure of environmental conditions. This again would tend to diminish the true strength of any relationship. If an admittedly imperfect measure gives an undoubted answer, then a more accurate criterion could only increase the significance of the result. This is being demonstrated in a current study[2] of the later growth and development of a sample of the surviving children born to these mothers. By regular domiciliary visits I am endeavouring to identify some features of the home environment, such as maternal care and nutrition, which are correlated with the health and growth of the child. These factors are quite highly correlated with social class, which thus serves an an indicator, albeit imperfect, of the real influences at work.

Since the writer rightly asserts that the Registrar-General's classification is not necessarily a good measure of economic status, it is strange that he should object to my efforts to remove obvious anomalies in this respect. My regrouping of miners (which is misreported and in any case only affected a small proportion of my cases) was designed to take account of the well-known fact that miners, especially in the Scottish lowlands, were a depressed community before the war, suffering long spells of unemployment, whereas the post-war miner is fully employed and relatively prosperous.

So much for phrase: "the interpretation of this finding is difficult" as a way of expressing denial of observed facts. On the interpretation of the findings, if accepted as genuine, your writer has little to say. He says that if childhood conditions really influenced prematurity risks we should be seeing a decline in recent years due to an improvement in nutrition during and after the war, but it is too early yet to make such an assertion, as girls born at the beginning of the war have only reached the age of 19. The majority of my mothers were born between 1925 and 1935 and reflect childhood conditions during the worst period of the depression. Finally, I would point out that the women and children about whom I have written are all seen by me personally and I have every opportunity of forming judgments and of checking the truth of what they tell me. They do not come to me merely as holes punched in a Hollerith card.—I am, etc.,

Edinburgh. C. M. DRILLIEN.

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1 Drillien, C. M., *J. Obstet. Gynaec. Brit. Emp.*, 1957, **64**, 161.
2 —— *Arch. Dis. Childh.* In press.

Home Confinement

SIR,—The experiences of an intelligent young mother before and after her first baby was born in the London area have come to my notice.

Expressing a strong wish for a home confinement, the parents were visited by "an inspector" (? health visitor) of the local health department. She gave them to understand that she would allocate the confinement to hospital or home as she saw fit, and that they should have no opinion or say in this decision. The verdict would be conveyed "in due course." There matters rested, and, despite regular attendance at local authority maternity clinics, six weeks before the baby was due the mother had no idea whether to prepare for a home confinement or not.

Moving then to another London district, she was accepted on the list of a doctor who expressed his interest in obstetrics. The case was now booked as a domiciliary, and persistent demands at clinic produced, less than two weeks before term, a visit from a midwife and a list of necessities. The confinement was attended by another midwife, two pupils, and a student as proxy for the doctor who had, they understood, undertaken to attend in person.

Care in the puerperium was shared between two midwives who must each have thought that the other was giving instruction in mothercraft. Certainly none was given. Two panic calls by the uninstructed parents were attended by different doctors (? assistant and principal) and after a fortnight all supervision of mother and child was left to local authority services.

The health visitor called early in the third week, inquired at the door after mother and child, and has not reappeared in the next five weeks. The baby cried a lot, causing anxiety to inexperienced

parents, the weight record at clinic was persistently unsatisfactory, and the briefest observation of the mother handling her baby showed her uncertain of herself and needing sympathetic guidance. In fact the only advice given was always to use boiled water for washing the baby's face, and that "babies always cry a lot." No instruction or supervision was offered, though the importance of regular attendance at clinic was stressed repeatedly. The mother was rated because she would miss one clinic while staying with a general practitioner's family. There, two days' common sense and precept restored peace and plenty.

If local authorities are determined to usurp the position of the family doctor in maternity and infant welfare, and make a fetish of clinic attendance, it would be well that the job were competently done from a family viewpoint, with adequate domiciliary supervision and consistent advice. It also seems unnecessary to pay doctors who leave their patients to such mass-production services at the same rate as those who, as is usual in rural areas, accept and carry out personally their responsibilities to the family.

It so happens that this patient is a French doctor's daughter. I wonder what her father now thinks of British maternity and infant care ?—I am, etc.,

Norwich. JOHN A. EDDINGTON.

Mercurial Diuretics and Nephrosis

SIR,—Clinical and necropsy findings similar to those described by Dr. Margaret Riddle and her colleagues and by Dr. J. Burston and his colleagues in your issue of May 31 (pp. 1274 and 1277) were noted in two adults who died in the Doncaster Royal Infirmary. The outstanding histological changes were damage of the proximal and distal convoluted tubules progressing to extreme flattening of the epithelium and dilatation of the lumen, which was filled with eosinophil debris. Minimal regenerative activity was noticed only in one of the cases.

This case, a man of 65, had recurrent swelling of the legs for five years as the result of myocardial fibrosis. He was treated with a course of mersalyl in 1952 and chlormerodrin in 1955 and 1956 respectively. When admitted on June 6, 1956, he had generalized oedema, fundi normal, blood pressure 120/80; serum albumin 1.1, globulin 3.8, g./100 ml.; electrophoresis showed a marked increase in the alpha and a slight increase in the beta globulin fraction and decrease of albumin and gamma globulin; serum cholesterol was 650 mg./100 ml. and blood urea 45 mg./100 ml. There was no response to mersalyl. He died on July 31 in uraemic coma. The necropsy findings were oedema of lower extremities, ascites, and a left pleural effusion, myocardial fibrosis resulting from coronary sclerosis. The kidneys weighed 480 g. and contained mercury, 2.8 mg. per 100 g. of weight; the renal venous blood contained 1.0 mg./100 g. Sarcoid granulomata were present in spleen and liver.

The second case was a male aged 48, treated with mersalyl several weeks prior to admission to hospital for cor pulmonale resulting from pulmonary emphysema. He died three days after admission.

An infant aged thirteen weeks which died from thrombosis of the dural sinuses following "enteritis" showed renal lesions identical with those seen following the use of organic mercury compounds. In addition, deposits of calcium phosphate were present in the necrotic cellular debris. In view of these rather suggestive findings the kidneys were submitted for analysis to Dr. A. Curry, who had carried out the previous analysis, and a level of 1.58 mg. mercury per 100 g. of kidney was obtained. Application of teething powders or calomel was denied by the parents.—I am, etc.,

Doncaster. H. LEDERER.

SIR,—It was with great interest that I read the papers in the *Journal* of May 31 by Dr. Margaret Riddle and her colleagues (p. 1274) and Dr. J. Burston and his colleagues (p. 1277) on the nephrotic syndrome following mercurial diuretic therapy. I wish to report a further such case, which I feel may be of additional interest in that it represents what is presumably a successful response to treatment of the fully developed syndrome with B.A.L. (dimercaprol).

A man, aged 66, was admitted to Queen Mary's Hospital, Roehampton, on July 19, 1956, complaining of progressive swelling of the legs of two months' duration, despite regular injections of meralluride sodium which he had been receiving, together with digitalis folia, gr. 1 (65 mg.) twice daily, ever since he had been an in-patient in June–September, 1955, with cardiac failure secondary to hypertension and myocardial ischaemia, with auricular fibrillation.

On the present admission he was not in cardiac failure, but showed gross generalized oedema, most marked in the lower limbs, and a left-sided pleural effusion. His blood pressure was now only 140/95, but there was well-marked cardiac enlargement and controlled auricular fibrillation was present: an E.C.G. showed, in addition, ventricular extra systoles and a left bundle-branch block. Gross albuminuria was present (8.6 g. per litre) and biochemical investigations confirmed the diagnosis of nephrotic syndrome. Total serum proteins were 3.6 g./100 ml., with albumin 1.5 g. and globulin 2.1 g. Electrophoretically, in addition to a low albumin, there was a marked increase in the alpha II and some rise in the alpha I globulins. The serum cholesterol was 470 mg./100 ml., and blood urea 57 mg./100 ml. Serum sodium, potassium, and chlorides were all within normal limits. Mercurial diuretics were stopped and he was treated with a high protein, low salt diet with little effect, until a course of dimercaprol was given (total dose 1.2 g. spread over six days) A most gratifying diuresis commenced three days after the initiation of this therapy and continued for almost three weeks after its completion, the urinary output being constantly between 90 and 110 fl. oz. (2.7 and 3.3 litres) daily. The oedema gradually subsided, while the blood chemistry concomitantly returned to normal limits with the ultimate disappearance of albuminuria. He was eventually discharged from hospital, the single course of dimercaprol only having been given.

When seen as an out-patient on December 17, 1956, he was oedema-free, with no albuminuria and with completely normal blood chemistry, there being no evidence whatever now of a nephrotic syndrome. He had been maintained on digitalis, but had had no further mercurial diuretics. The biochemical response to treatment at this stage may be summarized as follows:

Date	Urine Protein (g./litre)	Serum Albumin (g./100 ml.)	Serum Cholesterol (mg./100 ml.)	Blood Urea (mg./100 ml.)
20/7/56	8·6	1·5	470	57
2–7/8/56	Course of dimercaprol			
20/8/56	1·5	2·2	370	38
14/9/56	1·0	3·1	320	44
10/10/56	Trace	3·1	230	30
12/12/56	Nil	4·8	170	39

He was readmitted on May 27, 1957, with acute on chronic bronchitis and cardiac failure, as a result of which there was now a trace of albumin in the urine, but the blood chemistry was still within normal limits. His condition gradually deteriorated and he began to have Stokes–Adams attacks, E.C.G. now showing auricular fibrillation and a varying left and right bundle branch block. He died in such an attack on July 19, 1957. At necropsy the heart weighed 864 g. and there was considerable enlargement of the left ventricle and dilatation of the right ventricle; serious coronary sclerosis was present, with occlusion to a marked degree in the right coronary artery and a thrombosis about 3 cm. down its course. There were congestive changes in all the viscera. Kidneys showed no naked eye evidence of disease, and the histological report (Dr. J. Kohn) was as follows: "Kidney sections show traces of tubular damage with regeneration. There is, however, no evidence of active tubular damage present. Glomeruli are intact. Scattered foci of small cell infiltration present. The kidney is grossly hyperaemic, probably due to the terminal cardiac failure."

One would say that the post-mortem findings, in relation to the kidneys, provide confirmatory evidence of a reversal of the nephrotic syndrome in this case.

My thanks are due to Dr. G. E. Hosking for permission to report this case.

—I am, etc.,

London, S.W.15. G. CLENNAR.

Treatment of Homosexuality

SIR,—Everyone interested in the problem of homosexuality will be grateful to Dr. J. A. Hadfield for his excellent paper (*Journal*, June 7, p. 1323) and for the very clear demonstration he has given of the causes of this disease. Such forceful examples of the psychological basis and the cure by psychotherapy should abolish once and for all the speculations regarding genetic factors (for which there is little or no evidence) and stop the old parrot cry that there are no records of cure. It is a little surprising to me that this should have been repeated in the Wolfenden Report when at least one witness gave details of cured cases, and still more surprising that it is still being repeated, although I reported fourteen cases of apparent cure some five months ago.[1] It is probably due to lack of clarity in my writing, but I do not remember mentioning as suggested in your annotation (*Journal*, June 7, p. 1347) that only cases of homosexuality showing shyness and neurosis were curable. These were selected as most likely to respond, in contradistinction to those with personality distortion who did not wish to change and to psychotic and alcoholic inverts who were not likely to recover. Those who appear perfectly normal without evident shyness or neurosis may be treatable also, but give no indication of the difficulty likely to be met.

Most experienced psychiatrists have records of cure amongst their notes, but are reluctant to publish them in case it damages their practice. Let us hope that now Dr. Hadfield has published his cases others will follow. Only those who have never treated homosexuals or not treated them properly have never known a cure.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

REFERENCE

[1] Allen, C., *Homsexuality*, 1958. Staples, London.

Out-patient Anaesthesia

SIR,—The technique described by Professor William W. Mushin and Dr. Peter W. Thompson (*Journal*, June 14, p. 1376) seems to be rather an elaborate attempt to dress up a highly explosive wolf in a non-inflammable sheep's clothing. When a non-explosive mixture is required, surely it would be more rational to use one of the recognized non-inflammable anaesthetics, rather than juggle with such a highly explosive agent as cyclopropane. Moreover, while all things may be possible, there must have been countless millions of dental anaesthetics administered in blissful ignorance of the pyrotechnical possibilities of the dental forceps, despite the fact that at various times every explosive agent known to anaesthetists has been used for dental cases. Indeed, I once witnessed the application of a red-hot poker to a private patient in a dental chair, in an attempt to cauterize a particularly obstinate bleeding-point while under general anaesthesia, and nothing happened except that there was some dense white smoke, and the patient had a rather sore mouth for several days afterwards.

The problem of out-patient anaesthesia is, of course, an old one which has frequently been the subject of discussion, generally without any very definite conclusions being arrived at. What with all the intravenous hypnotics, analgesics, relaxants, tranquillizers, hypotensive agents, and other lethal drugs (not to mention their equally lethal antidotes), one cannot altogether blame the young anaesthetist of to-day if he occasionally lets enthusiasm outrun discretion.

So far as minor surgery is concerned, nitrous oxide and oxygen remains the anaesthetic of choice in most out-patient departments. Naturally, the results depend on the skill and experience of the administrator; but it is surprising how much can be achieved if the anaesthetist has taken the trouble to master the correct technique. When a supplementary agent is required cyclopropane is a most valuable anaesthetic, while trichloroethylene also has its uses. During the past 12 months I have been very favourably impressed with halothane, which has the advantage of being non-explosive. When administered in low concentrations of 1 to 1.5% halothane appears to be a safe and trouble-free anaesthetic, especially when a light or moderate plane of anaesthesia is required, as in most minor surgery; so far as my own experience goes, it may be administered to all sorts and conditions of patients ranging from infancy to extreme old age. Post-operative recovery is rapid and free from unpleasant after-effects. Halothane is also extremely useful as a supplement to nitrous oxide and oxygen in dental anaesthesia. It may conveniently be administered by means of a Rowbotham inhaler attached to the nitrous oxide apparatus: 2 or 3 ml should be sufficient for a dental clearance lasting 10 minutes or longer.

The principal objection to halothane is its relatively high cost (about 10d. per ml.), but with greater experience and improved technique it may be possible to remedy this in time. In this respect it would be interesting to compare halothane with the cost of cyclopropane/helium and oxygen, including the special cylinders required for the latter.—I am, etc.,

Newcastle upon Tyne. PHILIP AYRE.

Tattooing

SIR,—Mr. Norman C. Lake's article on tattooing (*Journal*, May 10, p. 1084) must have been read with interest by many. In a mixed surgical practice abroad for a good many years I became familiar with the tattooing favoured by South Indian Tamils. This took the form of an intricate pattern of intertwined loops, black in colour, occupying a large part of the dorsum of the hand, and very similar in design to the decorative chalk pattern often traced daily on the Indian hearth. The next most popular figures were crudely outlined scorpions and peacocks, also on the hand. The most original Tamil tattoo that I have seen (more than once) was a representation of a watch and strap tattooed on the wrist.

The British soldier in India was a great patron of the bazaar tattooist, and I have seen a queue of men from a newly drafted unit awaiting their turn outside a tattooist's in Secunderabad. In addition to the frequent designs mentioned by Mr. Lake, a favourite of the British soldier was a large topee with drops of falling sweat, with a diminutive pair of legs with puttees and boots beneath, rounded off with the motto "India Never Again." This ensemble was usually situated on the upper arm or upper leg.

A fairly popular method of erasing the names of displaced favourites is the superimposition of a compact pictorial design, such as a Chinese dragon.

A frequent justification offered by the Service man for his tattooing was that it was "as good as inoculation" in the prevention of illness. Only this week I examined a man who had been extensively tattooed years ago in India. He informed me that this was done as a cure for boils, on the advice of a sub-assistant surgeon, and with complete success, as he had "never had a boil since."—I am, etc.,

Deal, Kent. W. B. ROANTREE.

Management of Respiratory Paralysis

SIR,—It is fitting that the recent account by Dr. J. A. Forbes (*Journal*, April 5, p. 798) of significant experience in respiratory paralysis due to poliomyelitis should have appeared from Melbourne's Fairfield Hospital. Relatively few overseas articles other than those of Barach *et al.*[1] and of Cherniack *et al.*[2] (referred to by Forbes) have stressed the value of the "mechanical cough"; and surely this needs stressing. How often is the bronchoscope being reached for when almost all that is needed are sufficient prophylactic coughs?

Regarding earlier work, much credit has been given (and rightly so) to Lassen, Ibsen, Ritchie Russell, and Spalding, and others for their lessons from experience with controlled respiration; but the valuable earlier work of Elam, Hemingway, Gullickson, and Visscher,[3] from the University of Minnesota Teaching Hospital, appears to have passed almost unnoticed. With oximetric control, these workers, in 1946, noted certain physiological aspects and with encouraging success used their "tracheotomy-inhalator" apparatus.[4]

This employed a positive pressure, effected hydrostatically. It was employed effectively not only in the acute crises of several epidemics but also in certain patients for protracted periods of many months.—I am, etc.,

Sydney, Australia. R. I. MEYERS.

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Dummy Tablets

SIR,—As a member of the British National Formulary Committee I should like to assure Dr. E. C. Atkinson (*Journal*, June 21, p. 1478) that his eminently reasonable request for dummy tablets to be included in the *Formulary* has been most earnestly and sympathetically considered at the last two revisions. No doubt it will be considered again at the current revision, and it might help the committee if correspondents could produce fresh arguments for and against.

I cannot summarize two long discussions, even if it were legitimate to do so, but the *Formulary* is intended to be a help to treatment and should include medicaments of proved or presumed value. It has to meet the needs of practitioners, students, teachers, the hospitals, the Forces, and many Commonwealth countries as well. This dictates the inclusion of many formulae for which the British G.P. has no use and the exclusion of some he might like, but this does not prevent him prescribing any preparation he thinks necessary.

The prescribing of dummy tablets is a more involved matter than Dr. Atkinson seems to think. In hospital controlled trials the inert tablets are made to look exactly like those under trial, and usually the prescribing doctor is ignorant of which tablet is being given. This technique is impracticable in general practice. I conducted one such trial for a well-known firm, but when a patient complained that one lot of tablets had some undesirable side-effect —e.g., constipation—I found I could not honestly offer him another set and assure him it was different—as he wished it to be—when I did not know whether it would be so or not. A G.P. who has no faith in what he prescribes cannot pass over any confidence to his patient. He may be "scientific" but has no art or human touch. I found I had to choose between honesty and impersonal science, so, having explained my difficulty to the firm, I passed the tablets to another practitioner who had out-patients at a hospital and thought that this would enable him to overcome the difficulties. However, he also found it impossible to combine integrity and scientific objectivity, and the firm finally told me that all the G.P.s conducting the trial had reached the same conclusion.

This does not mean that I am against therapeutic trials in general practice. Indeed, I think them most desirable and have actually presided at three week-end conferences of G.P.s entirely devoted to this subject. What it does mean is that we have not yet found the correct technique to make the best use of the scientific acumen of the G.P. in his peculiarly intimate human relations for the clinical assessment of therapeutic effect. It is a vastly more complicated matter than any of the hospital and specialist trials of which we read, and personally I agree, regretfully, that it would be wrong for the *B.N.F.* to include a dummy tablet which might give a G.P. the illusion that he could use it for a trial that could in any way compare with them. I know a few cynics would say that the *B.N.F.* includes too many inert preparations already.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

Medical War Crimes

SIR,—I was astonished and profoundly disturbed to read that Dr. Herta Oberheuser has been permitted to resume practice in Germany, and strongly support the suggestions of Dr. M. H. Armstrong Davison (*Journal*, May 10, p. 1121) and Dr. Wilhelmina C. Maguire (*Journal*, June 14, p. 1420) that a protest should be made against this incomprehensible decision.—I am, etc.,

Radyr, Glamorgan. G. E. GREVILLE WILLIAMS.

Obituary

Sir ARNOLD STOTT, K.B.E., F.R.C.P.

Sir Arnold Stott, formerly senior physician to the Westminster Hospital, died suddenly after a long illness at his home near Guildford. He was 72 years of age.

Arnold Walmsley Stott was born on July 7, 1885, at Bardsley in Lancashire. He was educated at Rugby School, Trinity College, Cambridge, and St. Bartholomew's Hospital. Qualifying M.R.C.S., L.R.C.P. in 1909, he held resident appointments at his own teaching hospital and at the Royal Chest Hospital. Returning to Bart's as demonstrator of pathology, he later became chief assistant to the children's department. Early in his career Stott took a special interest in the study of cardiovascular diseases, and was one of the enthusiastic team of young physicians who were privileged to work with the late Sir Thomas Lewis. Later he became cardiologist to the Royal Chest Hospital and chief assistant to the electrocardiographic department at St. Bartholomew's, and students much enjoyed his lucid lectures on this new development in cardiological diagnosis. He was also appointed honorary physician to the Western General Dispensary. In 1912 he took the M.R.C.P. and in 1917 graduated B.Ch. at Cambridge.

[Walter Stoneman

Stott's career as a consulting physician was interrupted by his service in the R.A.M.C. during the first world war, during which he served as a major in the British Expeditionary Force. It was not long, however, before he was again immersed in hospital work and private practice.

W. E. L. writes: The medical staff at Westminster had become greatly depleted during the first world war, and in 1919 two vacancies on the medical side were filled by the election of the late Sir Stanley Woodwark and Arnold Stott. A year later Adolphe Abrahams was also elected to the staff, and there were also new appointments on the surgical side. At that time the Westminster medical school was a small one, and the thriving medical school of to-day owes much to the hard work done by the staff in the immediate post-war period. Stott established a department of electrocardiography at the hospital, but, eminent cardiologist as he was, he was also a general physician in the fullest and best sense of the term. He had a calm and kindly approach to patients, who soon felt the greatest confidence in his judgment and treatment. As a teacher he was excellent, and his instruction at the bedside gave students on his firm the very best introduction to clinical medicine. He aimed at developing the students' own powers of observation and he demanded a high standard in the clinical notes taken by his clerks. Although his comments were often critical, and at times even caustic, those who were his clerks will always remember the principles of clinical medicine as taught by their chief.

Elected a Fellow of the Royal College of Physicians in 1927, he later examined for the Conjoint Diploma as well as at Cambridge. He was a well-known figure at the College, and many Fellows will recall with pleasure his work for the Fellows' Club, of which he was secretary for many years. He also took the greatest interest in the Association of Physicians and rarely missed a meeting. In 1937 he was appointed Physician to the Royal Household.

During the building of the new Westminster Hospital, Stott's advice on many problems was greatly valued. The hospital was opened in May, 1939, but he was to work only for a short time at the new hospital, for as soon as war was declared in September, 1939, he was appointed consulting physician to the British Expeditionary Force with the rank of colonel and was in France until the evacuation of Dunkirk. On his return to England he played an important part in the organization of the medical services in the country, and he was promoted to major-general in 1942. For his distinguished services to the Army he was created a K.B.E. in 1946, and on his retirement from the Army service he was appointed honorary consulting physician to the Army. He was appointed Extra Physician to the Royal Household in 1948.

On his return to Westminster Hospital, after the war, Sir Arnold did not spare himself in the service of the hospital during the difficult post-war years and also in the early days of the National Health Service. His colleagues will always remember his chairmanship of the medical committee and will recall those brilliant flashes of humour which did much to enliven the meetings. He was indeed an ideal chairman. He was also for many years secretary of the staff dining club, and he was an excellent after-dinner speaker. Always an advocate of the view that a busy doctor should find time for recreation, he was himself an expert fly-fisherman and later was equally successful as a gardener. He retired from the staff of Westminster Hospital in 1950, and, although living at Guildford, he still carried out many of his former activities until failing health prevented his doing so.

We extend our sympathy to Lady Stott, his two daughters, and his son, the Rev. J. R. W. Stott, who as rector of All Souls, Langham Place, is well known to many living in the Harley Street area.

Dr. RAE GILCHRIST writes: Many tributes, public and private, will be paid to the memory of Arnold Stott, for he had many friends and many admirers. He was endowed with great gifts—a charm of manner, a flair for friendship, a quick sympathy, and a ready understanding. All these were qualities which endeared him to his patients, friends, and colleagues and quickly won their loyalty and devotion. An outstanding clinician, he had an unusually active and alert mind and was a keen and accurate judge of character. His loyalty to his colleagues, seniors and juniors, and the steady encouragement he gave to many younger men, was a side of his character less well known but none the less real. In a remarkable way, and quite unassumingly, he did an immense amount to promote the professional advancement of many of his junior colleagues throughout their careers and for as long as it was possible for him to help. There must be many who look back on their association with Arnold Stott with a deep-seated satisfaction and a heartfelt thankfulness for his very real friendship, his unfailing kindness, and for all his unassuming help and guidance through the years. Perhaps the contemplative mood of the angler and the satisfactions of the river bank contributed to his sympathetic understanding of human frailties and human endeavour. Certainly his election to the presidency of the Flyfishers' Club gave him immense pleasure. What a charming dinner companion he was! His appreciation of good food and wine, his pretty wit, his lively anecdotes, and his sound common sense made him the happiest of companions and the most agreeable of men.

DAVID HARVEY, C.B., C.M.G., C.B.E., M.D.

Major-General David Harvey, formerly director of pathology at the War Office, died at his home at Bembridge, Isle of Wight, on June 11. He was 86 years of age.

David Harvey was born at Glasgow on December 9, 1871, and was educated at the Greenock and Glasgow Academies. He then went on to Glasgow University to study medicine and was awarded a Lorimer bursary. Graduating M.B., Ch.B. in 1898, he proceeded to the M.D., with high commendation, in 1911. He joined the R.A.M.C. in 1899 and served in South Africa from 1900 to 1902. On his return to England he spent two periods (1903 and 1906) as assistant professor of pathology at the Royal Army Medical College. He was a member of the commission of inquiry into enteric fever in India from 1906 to 1908, and of the Royal Society's Commission which investigated sleeping sickness in Nyasaland from 1911 to 1913. In 1909–10 he was an Honorary Surgeon to the Viceroy of India. Harvey had a distinguished career in the first world war. For his services he was appointed C.M.G. in 1917 and C.B.E. in 1919. In the latter year he was appointed deputy director of pathology at the War Office, holding the post until 1923, when he was sent to Gibraltar as deputy director of medical services. His stay at Gibraltar was short, however, for later in 1923 he was recalled to London to become director of pathology at the War Office. From 1926 to 1930 he was an Honorary Surgeon to the King. When he retired from the Army in 1930 he was appointed C.B. For the next four years he was lecturer in tropical hygiene at the Liverpool School of Tropical Medicine. He also examined for the diplomas in public health and tropical medicine for the universities of Glasgow, St. Andrews, London, and Liverpool. From 1938 to 1945 he was a civil defence warden at Bembridge.

[*Bassano, Ltd.*

Harvey was assistant editor of the *Journal of the Royal Army Medical Corps* from 1916 to 1922, and he contributed the chapter on enteric fevers to Byam's *Tropical Medicine*. As a young man he was a keen athlete, and played rugby for his university from 1893 to 1898, being captain in his last year. He was also a member of the Scottish international athletics team against Ireland in 1898. He married Miss Fanny Gibson in 1902, and had three sons and one daughter. His second son is Air Vice-Marshal Sir George Harvey.

We are indebted to Colonel A. C. H. GRAY for the following appreciation: I first met David Harvey in 1906. I had brought Tulloch home from Uganda in an early stage of sleeping sickness, and I got Harvey to look at him, but in those early days no drugs seemed much use and our efforts were in vain. I next met him in 1914 when I was posted to the Royal Army Medical College as assistant professor of pathology—Harvey was there in charge of the typhoid vaccine department. As soon as war broke out Leishman and Cummins left for France and I joined Harvey in making the vaccine. We had to work night and day to meet the demands. We had no time to go to the mess for lunch, but Harvey was quite a good cook and with the aid of the lid of a biscuit tin and a bunsen burner produced excellent toasted cheese. When the war was over Harvey went to the War Office as Deputy Director and I joined him as his assistant. To say that Harvey was popular with his staff is a gross understatement: we all loved him dearly. I know that his one great regret was that he could not get out to France in 1914, but then he was invaluable at home.

J. S. K. B. writes: Few officers of the Royal Army Medical Corps can have been held in greater or more affectionate esteem by their colleagues, both senior and junior, than was Major-General David Harvey. Those of us who knew him in his later years of service recall a man of remarkably youthful appearance, so youthful that, to their sub-

sequent embarrassment, strangers not infrequently took him to be an officer of junior status, and accosted him as such. He was a man of few words and of a somewhat shy and diffident manner, but his friendly smile quickly put visitors at their ease, and his obvious desire to be helpful dispelled any lingering sense of officialdom engendered by the austere corridors of the War Office. As a young man he served under Sir David Bruce in the Sleeping Sickness Commission of the Royal Society which investigated the epidemiology and aetiology of that disease in Africa in the early years of the century. Later, in India and at home, he worked on the prevention of typhoid fever and on the preparation of prophylactic vaccine. Others who were associated with him in this work are better qualified to write of it than I am, and I will content myself by saying that when he talked of these subjects he displayed a depth of knowledge which surprised and sometimes shamed his younger colleagues. I knew him best during his term of duty in the War Office, where he was at first assistant to Sir William Leishman and later succeeded him as director of pathology. Harvey was an able administrator as well as a good pathologist. It was at this time that the new pathology service of the Army was born and grew to maturity, and Harvey's wise and tactful guidance, backed by his practical experience, played no small part in steering the new department through its early years. The status which it now enjoys is a monument to the success of his efforts.

R. F. HAYES, L.R.C.P.I., L.R.C.S.I.

Dr. R. F. Hayes, who turned from medical practice to politics and then to history and literature, died at his home at Dun Laoghaire on June 16. Until a few years ago he held the office of Film Censor in Eire.

Richard Francis Hayes was born in County Limerick and qualified from the Royal College of Surgeons in Ireland in 1905. After holding resident appointments he practised for some years near Dublin, but as an ardent nationalist he was drawn into the vortex of violent political action and imprisoned for his part in the Rising of 1916. While he was in Reading gaol he was elected M.P. for East Limerick, and he was released in 1919. He contested two further elections, but retired from active politics in 1923. Thereafter, though he continued in medical practice for some time, he became increasingly immersed in historical studies, particularly of the part played by Irishmen in French history.

Of Dr. Hayes a colleague has written as follows: My recollections of Richard Hayes go back to our first meeting half a century ago, when I was a raw pupil beginning my first practical lessons in clinical midwifery at the Coombe Lying-in Hospital during the mastership of Michael Gibson. Hayes had only recently been appointed as extern assistant to the master, having come on at the close of his term as house-physician at the Mater Misericordiae Hospital. First impressions in youth can be lasting, and Hayes's guidance of our novice hands in difficulty as we attended the mothers "on the district" was of the gentlest kind: his quiet voice, encouraging both the student and his "case," his gentle handling of the parturient mother, often in the most unfavourable domestic surroundings, his calm yet watchful concern for the safety of mother and child, made an unforgettable impression on every pupil who had called for his assistance. That quiet, informed capacity of service and of willing help remained a characteristic feature of the man through life. To us resident pupils in the hospital, most of whom in those halcyon summer days were from overseas—the writer was the only Irish student in residence through that long vacation—he appeared to be a reserved personality, for ever to be found, when wanted, reading Irish history in his room. He gave one the impression that his youth had perhaps "been delicate": in our "off hours," spent bathing or on the cricket field, he was, by comparison, almost a recluse. Hence we never came to know him intimately, nor yet to suspect the inner fires of Irish national sentiment that burned within him. Thus it came as a surprise, a few years later, to find that he had taken a soldier's rather than a scholar's part in the Rising of 1916, and, taken prisoner, had been sentenced to 20 years' imprisonment for his active part in an attack upon a Constabulary barracks in North Co. Dublin.

Hayes was born in Limerick, and the story of Sarsfield and of the "Wild Geese" who had followed that picturesque hero to join the armies of Louis XIII in France had an unending attraction for him. For a number of years he served as medical officer in the Donnybrook and Skerries dispensary districts on the outskirts of Dublin, his evenings spent in the pursuit of studies of these men and their descendants. Eventually, the pursuit of letters won him from medicine. His first book, *Ireland and Irishmen in the French Revolution*, appeared in 1932, followed by the more attractive *Irish Swordsmen in France* two years later. (The earlier book appeared in a Gaelic translation in 1933.) Others followed: *The Last Invasion of Ireland* (1937) and *Old Irish Links with France* (1940). His authoritative and scholarly exposition of the many historical bonds between the two countries gained for him the honorary D.Litt. of the National University of Ireland in 1941; ten years later the French Government awarded him the Cross of the Legion of Honour "in recognition of his literary services."

A Member of the Royal Irish Academy and of the Irish Academy of Letters, he was one of the most enthusiastic supporters of the Military History Society of Ireland. For ten years (1944–54) he filled with tact and good humour the office of Film Censor. He wrote no more books, but was a frequent and welcome contributor to the more serious Irish literary periodicals. A sound scholar, and in no sense a recluse, he was essentially a "man of his study," a friendly and helpful critic of other men's published work, one to whom the less well informed writer or essayist never turned in vain for assistance, one who gave gladly and generously of his own deep store of knowledge. May earth lie lightly on him!

E. K. WESTLAKE, M.A., M.D., M.R.C.P.

Dr. E. K. Westlake, senior medical registrar at the Middlesex Hospital, was found dead at his home in London on June 18. He was 33 years of age.

Ernest Keith Westlake was born on November 21, 1924, the son of Dr. A. T. Westlake, and was educated at Leighton Park School, Reading. His career as a medical student was outstandingly successful, for he won a major scholarship in natural science to St. John's College, Cambridge, and then took first-class honours in both parts of the Natural Sciences Tripos, being awarded the Hughes and Wright prizes. Going on to the Middlesex Hospital with a university entrance scholarship in 1946, he graduated M.B., B.Ch. in 1949, took the M.R.C.P. in 1953, and proceeded to the M.D. in 1954, winning the Horton-Smith prize. After graduation he went first to the Poole General Hospital as house-physician, returning to the Middlesex as house-physician to the neurological department. His next appointment was that of senior house-physician at the Chase Farm Hospital, and from there he went to the Brompton Hospital as house-physician. At Chase Farm Hospital he undertook a series of clinical and biochemical observations on emphysematous patients, and continued this study after his appointment as research assistant in respiratory physiology at the Institute of Diseases of the Chest. In 1952 he was awarded an Ernest Hart Memorial Scholarship by the B.M.A. He returned to Chase Farm Hospital for a time as medical registrar and then went on to a similar position at the Postgraduate Hospital, Hammersmith. At the time of his death he had been senior medical registrar at the Middlesex Hospital for over a year.

As a scholar, research worker, and clinician Keith Westlake had already made his mark. He was a tireless worker and had some notable publications to his credit. One of the first was a short report to this *Journal* on "Congenital

Indifference to Pain": this aroused much interest. In later years he wrote papers on emphysema which were published in the *B.M.J.* and in the *Quarterly Journal of Medicine*, and he contributed an article on "Dangerous Bronchitis" to the series on emergencies in general practice published in this *Journal* in 1955.

Dr. Westlake was married and had two daughters. To his widow and family we extend our sincere sympathy in their bereavement.

J. G. S. writes: Dr. Westlake's untimely death has cut short a career which, judged from its initial achievement, was full of promise. He had a distinguished record as an undergraduate, and after qualification soon showed an interest in research. The investigatory work on the disordered gaseous metabolism in emphysema that he started with Dr. Tom Simpson at Chase Farm Hospital and continued in the Institute of Diseases of the Chest, Brompton Hospital, was incorporated in the Cambridge M.D. thesis for which he was awarded the Horton-Smith Prize. He continued work on this problem during his tenure of an appointment as registrar at the Postgraduate Medical School of London. After this he moved to registrar and senior registrar appointments at the Middlesex Hospital, where his research interests underwent a logical change from the disturbances in gas metabolism associated with respiratory failure to the renal adjustments to respiratory acid-base disturbances. He set himself very high standards and obtained his results in research by close application and tenacity. Westlake tended to give an initial impression of diffidence, but this was probably a reflection of his self-critical personality. Those with whom he worked over long periods found him a loyal colleague and a helpful and stimulating collaborator.

C. H. G. BEKENN, M.B., Ch.B.

Dr. C. H. G. Bekenn, who had been in general practice at Sedgley, Staffordshire, for more than thirty years, died at his home there on June 8. He was 55 years of age.

Cyril Hector George Bekenn was born at Durban, Natal, on September 9, 1902, and was educated there at Hilton College. His parents returned to England, and he entered Birmingham University as a medical student, and graduated M.B., Ch.B. in 1924, being awarded the Foxwell memorial medal for clinical medicine. He represented the university in the cricket and tennis first teams. After a period as house-physician at the former Queen's Hospital, Birmingham, he entered general practice and succeeded the late Dr. S. Ballenden at Sedgley, a township where, two generations previously, an enterprising member of his family had also practised, keeping his own calf for the production of lymph for the inoculation of his patients against smallpox. Dr. Bekenn interested himself greatly in the work of the Soldiers, Sailors and Airmen's Association, and in the local branch of the British Red Cross. He was police surgeon for thirty-two years, and during the last war acted as medical officer of health for the district.

R. L. M. writes: Apart from his professional interests, Cyril Bekenn greatly enjoyed his tennis and dry fly-fishing for trout in Wales, especially the latter. Bird-watching, too, claimed some of his time. Of late years gradually developing ill-health began to limit his activities remorselessly, and he had to restrict himself to near-by visits to patients, or to his house. He was the ideal family doctor: with a pleasant and positive personality, clear speech, and ready smile, he radiated confidence and gave courage to his patients. His history-taking and examinations were indeed thorough, and he delighted in his knowledge of whole family groups and their relationships. It was always a pleasure to observe the complete trust his community placed in his judgment of their needs. For his funeral, it seemed as if almost the whole township appeared on the pavements to line the route from his house to the church, already thronged by a great congregation of sympathizers, to pay their respects. And one, politically poles apart, was heard to say that in Cyril Bekenn's death Sedgley had lost the best friend it had had in twenty years. He leaves a widow, a daughter of the late Dr. G. Percy Smith, of Birmingham. His elder son is in the Colonial Service in East Africa, while his younger son is about to take his place in the practice. His daughter is an orthoptist at the Eye Hospital in Birmingham.

J. A. DOUGLAS THOMPSON, M.B., Ch.B.

Dr. J. A. Douglas Thompson died on May 27 at Friston, near Eastbourne, where he had been living in retirement. He was 82 years of age.

John Andrew Douglas Thompson was born in Wigtownshire on July 12, 1875, and studied medicine at Edinburgh University, where he graduated M.B., Ch.B. in 1899. After holding a number of resident appointments in the Edinburgh area, he then travelled abroad as personal medical attendant to a patient and thus saw a great deal of the world. About this time his own health began to suffer, and after two serious illnesses he took up an appointment as a ship surgeon for two years. Dr. Thompson first entered general practice at Morley, near Leeds, in 1904, but in the following year he moved to Halesowen, Worcestershire, where, among other appointments, he was physician to the Anstey physical training college and medical officer to the old Midland and Great Western Railways. He was also an honorary surgeon to the St. John Ambulance Brigade, ultimately becoming corps surgeon. Rejected for active service in the first world war, he was in charge of the 1st Southern Auxiliary Hospital and the Romsley Hill sanatorium, while still conducting his own practice. He left Halesowen in 1925 and took a practice at Kenilworth, Warwickshire, where he remained for sixteen years, and where he was medical officer and public vaccinator for the district and honorary medical officer to the Kenilworth convalescent home. He left Kenilworth after a serious illness owing to overwork during the second world war, for he was area commandant for civil defence as well as a busy general practitioner. In 1943 he took another practice at Chipping Campden, Gloucestershire, but three years later ill-health forced him to retire, and he went to live at Friston. During his retirement he worked from time to time as locumtenent during the holiday season, and he retained his lifelong interest in first-aid by giving lectures and judging competitions, and as an examiner. Throughout his long life Dr. Thompson was one to whom anyone needing help instinctively turned. The letters written to his family at the time of his death all testified to the fact that his life's aim, "to heal and comfort," was fulfilled.

Medical Notes in Parliament

FUTURE OF CHARING CROSS HOSPITAL

The objections, local and general, to the proposal to rebuild Charing Cross Hospital and Medical School on the site of the present Fulham Hospital—itself due for reconstruction—and some assurances that had been given by the Board of Governors of Charing Cross, were set out in an adjournment debate in the House of Commons initiated by Mr. MICHAEL STEWART (Fulham, Lab.) on June 17.

The objections Mr. Stewart produced were these. There was provision at present for some 950 beds in all. If the proposal to transfer Charing Cross to the site were proceeded with there would thus be a loss of at least 150 beds to the people of Fulham and neighbourhood. Secondly, a teaching hospital could not provide the same facilities for Emergency Bed Service cases as an ordinary hospital. A teaching hospital in the area would be unlikely to take more than 200 E.B.S. cases in a year, compared with the 700 dealt with at the Fulham Hospital last year. Thirdly, although some provision would be made for treating the

elderly, it could not be equal in scope to the geriatric unit included in the original plan for the rebuilding of Fulham Hospital. A fourth point was that a teaching hospital, by its nature, must have a higher proportion of unusual cases than the average, and must therefore draw its patients from a wider area. That meant that a teaching hospital, if it was doing its job properly, could not have the same proportion of beds available for people in the neighbourhood. To these objections Mr. Stewart added the argument that the needs of Charing Cross Hospital and Medical School would be better met by proceeding with the earlier suggestion that it should be rebuilt in the Harrow area, where the site was to have been 47 acres instead of the nine at Fulham, and where there was a need for more hospital beds. About 75% of general practitioners in Fulham who were asked their opinion were opposed to the new proposal. In discussions in the B.M.A. marked hostility had been expressed, partly because of the decline in beds in the inner London area that it would mean, and partly because of the reduced facilities for emergency cases. The Fulham and Kensington Hospital Management Committee had also expressed its strong opposition to the proposal.

Reconciling Fulham's Needs with the Teaching of Medicine

Mr. RICHARD THOMPSON, Parliamentary Secretary, Ministry of Health, said the proposal—it was no more at present—raised two important considerations which he hoped they could reconcile when the final arrangements came to be made: first, the best way of organizing medical education in the University of London; and, second, the provision of an adequate hospital service in Fulham. The University and the University Grants Committee had reconsidered their acceptance of the Goodenough Committee's proposal in 1944 that the Charing Cross Hospital should move to Northwick Park. They now took the view that a solution must be found not involving so distant a separation from other university life and centres. There was also the point that the university statutes contemplated that all its institutions should be within the administrative County of London.

There was an urgent local need in Fulham for improved hospital facilities, and the demolition and rebuilding of the Fulham Hospital had already been agreed on. The Fulham site was closer to the university, and was also within the County of London. The rebuilt Charing Cross would eventually replace the existing Fulham Hospital, and also Fulham Maternity Hospital and the West London Hospital. The early regrouping of hospitals would take place, so that the Charing Cross governors could start work in Fulham.

The agreement of the South-west Metropolitan Regional Hospital Board was subject to two considerations: that the new hospital should provide district services comparable with those in the earlier plans for the redevelopment of Fulham; and that the position of the staff should be safeguarded. The board of governors of Charing Cross had given assurances that in consultation with the regional board a service fully adequate to the needs of the Fulham area would be provided, and that it would accept the transfer of the staff involved. The modern tendency in a teaching hospital was to provide a greater variety of patients to familiarize students with normal types of cases, as well as the more complicated. There was no reason to think a teaching hospital could not provide a district service in addition to fulfilling its teaching function. He did not think the anxiety over the Emergency Bed Service was justified.

It was proposed that the new Charing Cross Hospital should replace Fulham with 382 beds, the maternity hospital with 28, and the West London with 238, a total of 648 beds which would ultimately be closed. It was unlikely that the original rebuilding proposal would have provided Fulham with more than 400 or 500 beds, even allowing for the closing down of the West London. The Charing Cross governors had in mind a hospital of 700 to 800 beds, with the usual range of specialties. It was proposed that 10% of the total should be allocated for the chronic sick—slightly lower than Fulham's present 87—and discussions had taken place about where more beds for the chronic sick might be provided. The Minister did not rule out a public inquiry, which Mr. Stewart had asked for before any decision was made, but was not entirely convinced that it was the best way to proceed. He hoped to come to a decision fairly soon.

ANSWERS TO QUESTIONS

Private Beds in London

Mr. H. HYND (Accrington, Lab.) asked the Minister of Health on June 16 how many private beds were now available in London hospitals and nursing-homes, compared with the number before 1939 and before the creation of the Health Service. Mr. WALKER-SMITH stated that at December 31, 1957, 2,255 beds were available under Sections 4 and 5 of the National Health Service Act, 1946, in the Metropolitan Police district. He understood that there were 2,288 beds classed as private beds in the same hospitals shortly before the inception of the Health Service, but, as there was then no accepted definition of the term "private," the figures were not strictly comparable. Information for 1939 and for institutions outside the Health Service was not available.

Sir GODFREY NICHOLSON (Farnham, Con.) thought the beds were not being used as much as they should be, and Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) said that the last figures suggested that almost one-quarter or one-third of them were not in use. Mr. WALKER-SMITH pointed out that there never would be 100% occupancy. The beds were used for their primary purpose, and there was also a proviso in section 5(1) of the Act which made them available for cases requiring attention. Taking the two things together, there was a reasonable use of these beds, but he would look at the matter and see whether anything could or should be done to promote the occupancy rate.

Bacteriology of Imported Egg Products

Captain H. B. KERBY (Arundel and Shoreham, Con.) asked the Minister of Health on June 17 if he was satisfied that Chinese white and yolk of egg, as at present imported into the United Kingdom, were fit for human consumption in view of analytical reports to the contrary. Mr. D. WALKER-SMITH stated that bulked egg products from any source were liable to contain pathogenic organisms, and for this reason they were sampled by port health and other local authorities for bacteriological examination. He did not think that special action in relation to Chinese egg products was required at present. The trade had arranged for dried crystalline albumen to be heat-treated before distribution.

Sir ALFRED BOSSOM (Maidstone, Con.) asked the Minister on June 20 if he would request the authorities in the exporting countries which sent liquid eggs to Great Britain to make appropriate hygienic and bacteriological examination during and on completion of packing, to ensure freedom from salmonella organisms existing in these foodstuffs. Mr. WALKER-SMITH, assuming that this referred to bulk egg, which was imported frozen, said several countries had been asked to take measures of the kind described, and the Government would continue to make such requests where the circumstances required it.

Doctors for Colonial Service

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) asked the Secretary of State for the Colonies whether he was aware of the shortage of doctors in the Colonial Service; and what steps he was taking to encourage young doctors from Great Britain to take appointments in the West Indies and other colonial territories. Mr. J. PROFUMO, the Under-Secretary, replying on June 17, said he was well aware of the constant demand for doctors in the medical departments of the overseas territories, which the Secretary of State was doing his best to meet. Vacancies in the West Indies and other territories were advertised in the professional journals as they were notified. In addition, special

arrangements had been made to allow applications from young doctors to enter the Colonial Service as an alternative to national service.

Mr. BLENKINSOP asked him to consider consultation with the teaching hospitals to see whether any kind of guarantee could be given to young men entering for temporary service that their chances of promotion in this country were not thereby spoiled. Mr. PROFUMO said that was something he would like to look at.

Mrs. LENA JEGER (Holborn and St. Pancras, South, Lab.) recalled that the Minister of Health had recently received a report suggesting that there should be a limitation on the intake of medical students. If this problem were brought before him he might take a different view of the standard of medical education. Mr. PROFUMO suggested that she should question the Minister of Health, but pointed out that there was the closest co-ordination between the two departments on this matter.

Recruiting for Hong Kong

Mr. BLENKINSOP asked what action was being taken to recruit suitable medical personnel for resident and visiting posts in the Hong Kong Medical Department and teaching posts in Hong Kong University. Mr. PROFUMO said that medical appointments in Hong Kong were made to a large extent locally. Such vacancies as were notified to the Secretary of State were normally advertised in the medical journals. Teaching posts in the Hong Kong University were filled independently by the university authorities.

Mr. BLENKINSOP said he understood the *British Medical Journal* had barred advertisements from Hong Kong because of the payment of different rates there to men and women in the service. Would the Secretary of State take the opportunity to review this and make the payments equal? Mr. PROFUMO explained that it was not a decision of the Secretary of State but of the Government of Hong Kong. Mr. BLENKINSOP pressed him to bring the matter to the attention of the Governor, and Mr. PROFUMO said the Secretary of State was in consultation with him, but it was a matter for the Hong Kong Government to decide.

Prescription Costs

The MINISTER OF HEALTH informed Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) on June 23 that the average cost of Health Service prescriptions last April was 6s. 4¼d.

Mr. BLENKINSOP asked if the Minister was satisfied that the arrangements made with the drug companies were working properly. Mr. WALKER-SMITH said he thought so, but he would keep them under review. Mr. BLENKINSOP asked if he would consider the recommendations of the Hinchliffe Committee that prices should always be included in the material sent by drug manufacturers to doctors. Mr. WALKER-SMITH replied that he was already giving active consideration to the report, and was in consultation about it.

Mr. A. KERSHAW (Stroud, Con.) asked whether the increased cost of prescriptions was due to the use of more expensive drugs by doctors, or to greater quantities of cheaper drugs. Mr. WALKER-SMITH said that an examination of samples in the last year showed that the expensive corticosteroid preparations which became available then and in 1956 were being increasingly prescribed. He thought it likely that this trend towards expensive preparations had continued, but it was not possible to say with regard to 1958.

Mr. W. HAMILTON (Fife, West, Lab.) asked for comparative costs in selected towns he named. Mr. WALKER-SMITH stated that the approximate average cost in March, 1958, was given in the following table, except for Worthing and Weston-super-Mare, which were not executive council areas, and for which separate figures were therefore not available:

	s.	d.		s.	d.
Bournemouth ..	6	8½	Hull	6	1½
Eastbourne	7	0	Sheffield	5	3½
Blackpool	6	9½	Leeds	5	9
Manchester ..	6	3½	Newcastle	6	10
Liverpool	5	8	Sunderland	5	10½

The average cost for the county executive council areas in which Worthing and Weston-super-Mare were included were: Sussex, West (includes Worthing), 7s. 0½d.; Somerset (includes Weston-super-Mare), 6s. 6½d.

Finance for Mental Health Service

Mr. BLENKINSOP asked what financial assistance was to be given to local authorities to enable them to establish and develop services for the care and welfare of such of the mentally sick and defective patients as could now be discharged from hospitals and institutions. Mr. WALKER-SMITH stated that expenditure by local authorities on the development of these services already qualified for specific Exchequer grant, and, on the assumption that the Local Government Bill was passed in substantially its present form, would be taken into consideration in the proposed new general grant. He had also informed local authority representatives that he proposed to assist authorities, where this was possible, by letting them have, for a purely nominal consideration, suitable small hospital buildings that can be spared.

Mr. BLENKINSOP said the administrative changes that the Minister had already proposed for mental hospitals would be rendered nugatory unless there was fresh provision of finance. Mr. WALKER-SMITH replied that where he could help was to recommend loan sanction for capital work in the mental health service at a higher level than in recent years, and that he proposed to do in the immediate future.

Medical Act Amendment.—The Medical Act, 1956 (Amendment), Bill passed the remaining stage without alteration in the House of Commons on June 20.

Rearward Facing Seats in Aircraft.—The Ministry of Transport and Civil Aviation has decided to set up a small working party, under the chairmanship of the Chief Aeronautical Adviser, to review the question of safety in rearward facing seats in aircraft.

Vital Statistics

Week Ending June 14

The largest rises in the notifications of infectious diseases in England and Wales during the week ending June 14 were 106 for whooping-cough, from 641 to 747; 91 for food-poisoning, from 184 to 275; and 53 for scarlet fever, from 613 to 666. The only fall of any size was 837 for measles, from 6,431 to 5,594. The largest decreases in notifications were 135 in London, from 592 to 457; 117 in Nottinghamshire, from 336 to 219; 101 in Warwickshire, from 290 to 189; 100 in Middlesex, from 553 to 453; and 90 in Somersetshire, from 211 to 121. The largest rise in the notifications of scarlet fever was 28 in Lancashire, from 71 to 99. Only small fluctuations were reported in the local trends of whooping-cough. No cases of diphtheria were notified during the week, compared with 2 in the preceding week. This is the second occasion when no cases of diphtheria have been notified; the first was almost two years ago.

The notifications of acute poliomyelitis numbered 29, and these were 4 more for paralytic and 6 fewer for non-paralytic cases than in the preceding week. The largest returns were Essex 6 (Chelmsford M.B. 2), Lancashire 4 (Manchester C.B. 3), and Yorkshire West Riding 4.

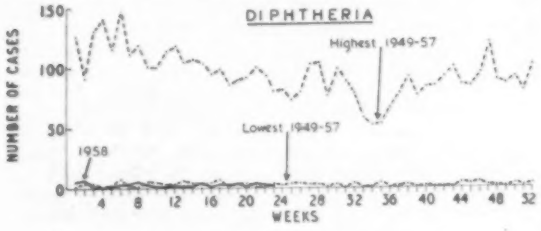
There were 891 cases of dysentery notified, 8 more than in the preceding week. The largest centres of infection were Yorkshire West Riding, with 171 notifications (Barnsley C.B. 37, Leeds C.B. 21, Rotherham C.B. 19, Huddersfield C.B. 18, Sheffield C.B. 17, York C.B. 13, Bradford C.B. 12), Lancashire 126 (Liverpool C.B. 36, Manchester C.B. 16, Oldham C.B. 15), Essex 69 (Chigwell U.D. 36, Walthamstow M.B. 19), London 65 (Wandsworth 13, Islington 11), Durham 60 (Easington R.D. 13, Hartlepool M.B. 12, Gateshead C.B. 12), Middlesex 53 (Twickenham M.B. 22), Hampshire 37 (Droxford R.D. 18, Havant and Waterloo U.D. 17), Nottinghamshire 37 (Nottingham C.B. 14), Surrey 35 (Banstead U.D. 20), Cambridgeshire 31 (Cambridge M.B. 31), Cheshire

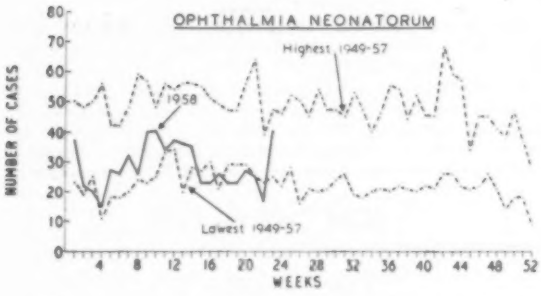
27 (Wallasey C.B. 10), Gloucestershire 27 (Bristol C.B. 24), and Warwickshire 25 (Bedworth U.D. 10).

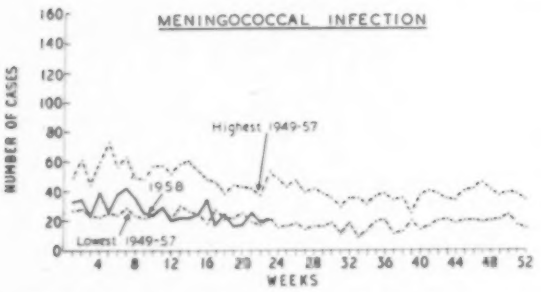
The largest outbreaks of food-poisoning during the week were Isle of Wight R.D., with 52 notifications, and Nottinghamshire, East Retford R.D., with 23.

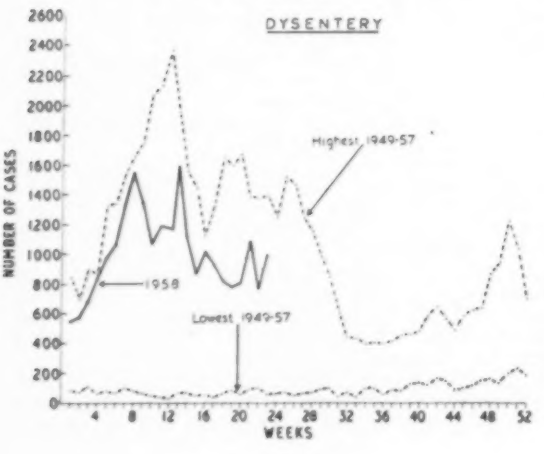
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **June 7** (No. 23) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	2	0	5	0	2	4	0	2	1	2
Dysentery	883	85	202	12	3	687	68	256	7	5
Encephalitis, acute	3	0		0		3	0		0	
Enteric fever:										
Typhoid	7	0	0	0		4	1	0	0	2
Paratyphoid	6	0	3(B)	0		2	2	0	0	
Food-poisoning	184	24	7	2		197	27	17	0	
Infective enteritis or diarrhoea under 2 years				12	15				21	22
Measles *	6,431	592	162	40	28	23,290	964	136	235	310
Meningococcal infection	20	0	8	0		26	4	8	0	1
Ophthalmia neonatorum	40	3	3	0		38	3	4	0	
Pneumonia †	264	18	126	11	1	326	19	153	6	1
Poliomyelitis, acute:										
Paralytic	16	0	6	2	7	48	7	4	5	2
Non-paralytic	15	0				26	2			
Puerperal fever§	203	31	10	1		214	28	11	0	
Scarlet fever	613	47	77	25	15	589	58	65	28	22
Tuberculosis:										
Respiratory	571	68	93	24		591	62	229	15	
Non-respiratory	97	10	16	1		86	6	22	7	
Whooping-cough	641	43	76	25	24	1,523	65	160	3	54

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	1	0		0			1		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	2	0	0	0	2		0	3	0	1
Influenza	7	0	0	0	2		0	1	0	0
Measles		0	0	0			0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	348	34	14	7	8		34	23	6	6
Poliomyelitis, acute	4	0		0	0		0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	64	7	6	0	4		7	7	1	1
Non-respiratory		0	2	0	0		2	0	0	0
Whooping-cough	0	0	0	0	0		0	0	0	0
Deaths 0–1 year	276	27	30	6	13		22	40	3	18
Deaths (excluding stillbirths)	8,838	718	547	119	161		717	547	93	149
LIVE BIRTHS	15,254	1258	956	234	378		1194	942	237	548
STILLBIRTHS	293	29	21				28	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Diamond Jubilee of R.A.M.C.—A service of thanksgiving, remembrance, and dedication was held in Westminster Abbey on the morning of June 24 to mark the diamond jubilee of the Royal Army Medical Corps (see *Journal*, June 14, p. 1405). The service was attended by QUEEN ELIZABETH THE QUEEN MOTHER, Colonel-in-Chief of the Corps; the Director-General, Army Medical Services, Lieutenant-General Sir ALEXANDER DRUMMOND; and many serving and former members of the R.A.M.C. The congregation completely filled the Abbey. The service opened with a fanfare of trumpets and the National Anthem. The sermon, preached by the Rev. V. J. PIKE, Chaplain-General to the Forces, was followed by the R.A.M.C. collect, which asked that "by loyalty in hard service after the manner of Luke the beloved physician [the Corps might] be found faithful in ministering to those in need." After the service there was a reception at the Royal Army Medical College, Millbank.

Royal College of Surgeons of England.—On June 11 the College held its first ceremonial presentation of diplomas. Professor C. F. W. ILLINGWORTH, of Glasgow, and Professor F. DE G. D'ALLAINES, of Paris, were admitted to the honorary fellowship, after citations in their honour by Professor IAN AIRD and Professor DIGBY CHAMBERLAIN respectively. Professor R. W. SCARFF, Air Vice-Marshal J. C. NEELY, and Professor F. C. WILKINSON, who had been elected fellows, were formally admitted. Diplomas were then presented to those who had been successful in the College's various examinations during the past year. Parties from each of the medical schools were received in turn by the president, Sir JAMES PATERSON ROSS, who handed them their diplomas. Some 200 diplomates were presented in this way in the presence of an audience which filled the Great Hall to capacity. At a council meeting the next day the following were co-opted to the College council for 1958–9 as representing various branches of practice: Dr. JOHN HUNT (general practice), Dr. FRANKIS EVANS (anaesthetics), Mr. T. KEITH LYLE (ophthalmology), Mr. A. C. H. BELL (gynaecology and obstetrics), Professor D. W. SMITHERS (radiology), Mr. C. GILL-CAREY (otolaryngology), Sir WILFRED FISH (dental surgery).

West London Medico-Chirurgical Society.—The president, Mr. A. E. ROCHE, was in the chair at the 68th annual dinner of the Society, the health of which was proposed by Professor ROBERT PLATT, P.R.C.P. The main aim of such a society as the West London Medico-Chirurgical Society, said Professor Platt, was to bring doctors together, and it was doing particularly good work when it brought various kinds of doctors together. The old boundaries which used to be so rigid were being broken down and there was much more awareness of the necessity to work in teams. A significant trend had recently become evident. General practitioners were now depriving specialists of large numbers of interesting cases which used to be treated in hospital. With modern methods of treatment the general practitioner could care for these patients in their own homes. Replying to the toast, Mr. ROCHE reviewed the year's activities—the 76th year of the Society's existence. The health of the guests was proposed by Mr. J. C. R. HINDENACH, who specially welcomed the Society's Cavendish lecturer, Sir GORDON GORDON-TAYLOR, describing him as a "humble, distinguished, and versatile man." The reply for the guests was made by Professor A. M. CLAYE, P.R.C.O.G., and Dr. MACDONALD CRITCHLEY.

Chancellor of Leicester University.—On June 20 LORD ADRIAN, O.M., F.R.S., was installed as Chancellor of Leicester University. After his installation Lord Adrian received the University's honorary D.Sc.

Three London Chairs.—London University announces the appointment of Dr. W. BLACKWOOD, to the university chair of neuropathology at the Institute of Neurology; Dr. J. N. CUMINGS to the university chair of chemical pathology at the Institute of Neurology; and Dr. N. F. MORRIS to the university chair of obstetrics and gynaecology at Charing Cross Hospital Medical School. Dr. Blackwood graduated at Edinburgh in 1934, obtaining the F.R.C.S.Ed. four years later. His present appointment is pathologist at the National Hospital, Queen Square, and he was previously senior lecturer in neuropathology at Edinburgh. Dr. Cumings graduated from King's College Hospital, London, in 1928, proceeding M.D. (London) in 1931. He obtained the M.R.C.P. in 1930 and was elected F.R.C.P. in 1953. He is clinical pathologist at the National Hospital, Queen Square. Dr. Morris graduated from St. Mary's in 1943, proceeding M.D. (London) and M.R.C.O.G. in 1949. After holding the post of first assistant to the obstetric unit at University College Hospital, Dr. Morris was appointed to the consultant staff of Hammersmith Hospital and became reader in obstetrics and gynaecology at the Institute of Obstetrics and Gynaecology.

Chair of Anatomy, St. Andrews.—Dr. R. E. COUPLAND, lecturer in anatomy at Leeds, has been appointed to the Cox Chair of Anatomy at St. Andrews University. He will succeed Professor D. RUTHERFORD DOW, who retires on September 30. Dr. Coupland graduated at Leeds in 1947, proceeding M.D. and Ph.D. He was appointed to a lectureship in anatomy at Leeds in 1950, where he has remained since, except for a period during 1955–6, when he visited the department of anatomy at Minnesota University as an assistant professor.

Oxford University.—Dr. H. R. VICKERS has been appointed to a university lectureship in diseases of the skin. Sir RUDOLPH PETERS, F.R.S., has been elected an honorary fellow of Trinity College. These appointments were reported in error last week (*Journal*, June 21, p. 1491) under the heading "Cambridge University."

Society of Apothecaries.—At a soirée on July 22 the Master of the Worshipful Society of Apothecaries of London will confer the Society's honorary freedom on Sir HENRY SOUTTAR, and the Galen medal in therapeutics for 1958 on Sir MACFARLANE BURNET, O.M., F.R.S.

William Cullen Prize.—The Royal College of Physicians of Edinburgh has awarded its four-yearly William Cullen prize to Professor W. MELVILLE ARNOTT, professor of medicine at Birmingham University. The prize was founded in the year of Queen Victoria's jubilee, and is awarded for "the greatest benefit done to practical medicine."

Edinburgh Prize for Women Doctors.—The Royal College of Physicians of Edinburgh invites applications for the Dr. Jessie Macgregor prize for medical women from graduates of Edinburgh University or holders of the Scottish triple qualification. The prize (value £75) is for the best record of original work in the science of medicine published not earlier than July, 1954 (or unpublished). Applications must be in the hands of the Convener of Trustees at the College by October 31.

Blood Transfusion Award.—The Oliver Memorial Fund's committee invites applications on behalf of candidates for the Fund's tenth annual award (value £50). The award is for notable original work or service by a British subject in the research, organizational, or donor fields of blood transfusion. Applications should be made to the Fund's hon. secretary, Mrs. F. E. BEDBOROUGH, 105, New Park Avenue, London, N.13, before September 30.

"Cerebral Palsy Bulletin."—The medical advisory committee of the National Spastics Society has launched a new quarterly, *Cerebral Palsy Bulletin*, by which it hopes to stimulate interest in the scientific and clinical aspects of the various forms of the disease. The first issue, said

to be atypical, includes a reprint of W. J. Little's classical account of cerebral palsy, first published in 1861. The *Bulletin*, with an editorial board headed by Professor A. V. NEALE, is obtainable from the National Spastics Society, 28, Fitzroy Square, London, W.1, price 12s. per annum.

COMING EVENTS

Royal Medico-Psychological Association.—Annual meeting, July 1–4, at Bexley and in London. Details from Dr. A. B. MONRO, 11, Chandos Street, Cavendish Square, London, W.1.

Bertram Louis Abrahams Lecture.—Sir LINDOR BROWN, F.R.S., will lecture at the Royal College of Physicians of London on July 8, at 5 p.m. His subject will be "The Mode of Action of Sympathetic Nerves."

F. E. Williams Lecture.—Professor P. B. MEDAWAR, F.R.S., will lecture at the Royal College of Physicians of London on July 10 at 5 p.m. His subject will be "The Biology of Ageing."

"Ars Medica."—The exhibition (see *Journal*, June 7, p. 1363) will be on view from June 27 to July 4 at Guy's Hospital; July 10–18 at the B.M.A. Annual Meeting at Birmingham; July 21–23 at St. Helier Hospital, Carshalton; and July 25–31 at Charing Cross Hospital Medical School.

Mackenzie Industrial Health Lecture.—Dr. A. MEIKLEJOHN will deliver the seventh Mackenzie industrial health lecture at Nottingham University on July 15, at 3 p.m. His subject will be "Industrial Health Meeting the Challenge." The lecture is sponsored by the B.M.A. in conjunction with the Association of Industrial Medical Officers.

William Meredith Fletcher Shaw Memorial Lecture.—Professor JAMES BLACK will lecture at the Royal College of Obstetricians and Gynaecologists on July 25 at 5 p.m. His subject will be "Reminiscences of Fifty Years' Medical Practice—Forty-Seven of Them in South Africa."

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Archives of Disease in Childhood.—Issued six times a year (£4 4s. annually). The new issue, Vol. 33, No. 169, includes :

ABO INCOMPATIBILITY AND HAEMOLYTIC DISEASE OF THE NEWBORN. G. H. Valentine.
THE DISAPPEARANCE OF FOETAL HAEMOGLOBIN IN CONGENITAL CYANOTIC HEART DISEASE. M. Coghlan and M. C. Joseph.
BASOPHILIC LEUCOCYTES IN CHILDREN IN HEALTH AND DISEASE. Ross G. Mitchell.
INTRAPERITONEAL BLOOD TRANSFUSION IN CHILDREN IN ACCRA, WITH SPECIAL REFERENCE TO THE TREATMENT OF KWASHIORKOR. Susan B. G. Ofori Atta.
TRAUMATIC SUBPERIOSTEAL HAEMATOMA OF THE FEMUR IN THE NEWBORN. Ross G. Mitchell and K. Rhaney.
SUBGLOTTIC HAEMANGIOMA: TWO INFANTS WITH LARYNGEAL STRIDOR. C. A. Ho'borow.
INTRASPINAL NEUROBLASTOMA IN A NEWBORN BABY. E. Elefant, V. Voita, and V. Benes.
SOME UNUSUAL FINDINGS IN A FAMILY WITH FRIEDREICH'S ATAXIA. Peter E. Sylvester.
A CASE OF INTRACRANIAL DERMOID CYST ASSOCIATED WITH THE KLIPPEL-FEIL DEFORMITY AND RECURRENT MENINGITIS. A. Peter Roberts.
SIRENOMELIA: SYMPUS DIPUS ("MERMAID"). Hugh Jolly and Edith M. Lamont.
GARGOYLISM: CLINICAL, RADIOLOGICAL, AND HAEMATOLOGICAL FEATURES IN TWO SIBLINGS. S. B. Griffiths and M. Findlay.
HYDRANENCEPHALY (HYDRENCEPHALY). L. Crome and Peter E. Sylvester.
THE WENCKEBACH PHENOMENON AND AURICULAR-VENTRICULAR DISSOCIATION IN CHILDREN. M. H. Shnier.
A SALT WASTING SYNDROME IN INFANCY. Donald B. Cheek and John W. Perry.
ANOREXIA AND SEVERE INANITION ASSOCIATED WITH A TUMOUR INVOLVING THE HYPOTHALAMUS. Helen Kagan.
ACUTE SPINAL EPIDURAL ABSCESS: A CASE IN AN INFANT WITH RECOVERY. R. G. Rushworth and P. B. Martin.
COW'S MILK ALLERGY IN INFANCY. W. Davies.
FRANK BERIBERI IN A 4-MONTH-OLD INFANT. Tadeusz Giza and Jerzy Armata.
WILLIAM HEBERDEN'S CASES OF ANAPHYLACTOID PURPURA. Arthur Rook.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature in the world. Annual subscription £4 4s.

Thorax.—Issued quarterly (£3 annually). The new issue, Vol. 13, No. 2, includes :

SELECTIVE ANGIOCARDIOGRAPHY OF THE RIGHT HEART. S. Holesh and H. M. T. Coles.
PERCUTANEOUS LEFT VENTRICULAR PUNCTURE WITH CATHETERIZATION OF THE AORTA. H. A. Fleming, E. W. Hancock, B. B. Milstein, and D. N. Ross.
THE PERIPHERAL PATTERN IN THE NORMAL BRONCHOGRAM AND ITS RELATION TO PERIPHERAL PULMONARY ANATOMY. Lynne Reid and G. Simon.
THE SECONDARY LOBULE IN THE ADULT HUMAN LUNG, WITH SPECIAL REFERENCE TO ITS APPEARANCE IN BRONCHOGRAMS. Lynne Reid.
CONGENITAL OESOPHAGEAL ATRESIA AND TRACHEO-OESOPHAGEAL FISTULA. K. D. Roberts.
EXTRAPERIOSTEAL PLOMBAGE IN THE TREATMENT OF PULMONARY TUBERCULOSIS. F. H. Young.
A PATHOLOGICAL STUDY OF EMPHYSEMA OF THE LUNGS WITH CHRONIC BRONCHITIS. Brian E. Heard.
THE PATHOLOGY AND BACTERIOLOGY OF RESECTED TUBERCULOUS LUNG LESIONS AFTER CHEMOTHERAPY. D. J. Cotter, H. M. Foreman, and R. M. E. Seal.
THE GASTRO-OESOPHAGEAL JUNCTION IN INFANCY. I. J. Carré and R. Astley.
A METHOD OF TREATING INFUNDIBULAR PULMONARY STENOSIS. A. Temesvári.
ELECTROPHORETIC ANALYSIS OF SEROUS PLEURAL EFFUSIONS. A. J. Taylor.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 30

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE.—5 p.m., Professor Isidor Greenwald (New York): History of Endemic Goitre: Its Significance for the Aetiology of the Disease.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. F. Goodwin: Combined Valvular Disease.
UNIVERSITY COLLEGE, Gower Street, W.C.—5 p.m., public lecture by Dr. J. D. Robertson: The Molecular Biology of Cell Membranes.

Tuesday, July 1

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. O'Neill: Emotional Aspects of Skin Diseases (2).

Wednesday, July 2

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. V. Gibson: Atrial Septal Defects.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. Enrique Ager Muguerza (Madrid): Carcinoma of the Epiglottis.
LONDON UNIVERSITY.—At Bearstead Lecture Theatre, London Hospital Medical College, 4.30 p.m., special university lecture in medicine by Professor T. Hale Ham (U.S.A.): Haemolytic Anaemia.
MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, Mill Hill, N.W., 5 p.m., Professor Samuel Graff (New York): Experiments with Continuous Metazoan Cell Cultures.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. F. Fulton: Tissue Culture for the Diagnosis of Virus Infections.

Thursday, July 3

●INSTITUTE OF CHILD HEALTH.—5 p.m., Sir F. Macfarlane Burnet, F.R.S. (Melbourne): Immunological Aspects of Early Life.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Mr. Norman Tanner: Haemorrhage from the Oesophagus.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. G. Melville Jones: Orientation in Flight.
●MIDDLESEX HOSPITAL MEDICAL SCHOOL.—At Clinical Lecture Theatre, 3.30 p.m., Professor Charles Huggins (Chicago): Cancer of the Prostate.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Board Room, West London Hospital, Thursday, July 3, 5.15 for 5.30 p.m., annual general meeting.

Friday, July 4

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION (PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION).—At Claybury Hospital, Woodford Bridge, Essex, 10.30 a.m., Dr. D. V. Martin and Dr. J. S. Pippard: Towards a Therapeutic Community—Problems and Development.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Mott.—On June 13, 1958, to Elizabeth (formerly Carson), wife of John H. Mott, B.M., B.Ch., of 4, Hilbre Drive, Southport, Lancs, a daughter.
Nettleton.—On May 20, 1958, at Middlesbrough Maternity Hospital, to Eileen, wife of Leon A. Nettleton, a son—Robin Alexander.

DEATHS

Acheson.—On June 3, 1958, at his home, Dunard, Aqueduct Lane, Alvechurch, Worcs, Samuel Acheson, M.B., B.Ch.
Barcsal.—On May 31, 1958, at 193, Queen's Gate, London, S.W., Abris Barcsal, M.D.
Bond.—On June 6, 1958, at Blackheath, London, S.E., Ashton Bond, M.D., D.T.M., formerly of Weybridge, Surrey, aged 84.
Elliott.—On June 4, 1958, Edgar Lionel Elliott, M.B.E., M.B., B.S., of The Old White Hart, Stokenchurch, Bucks.
Isaac.—On June 6, 1958, at her home, 8, Stanley House, 103, Marylebone High Street, London, W., Marjory Isobel Hay Isaac, M.B., Ch.B., D.P.H., aged 43.
Merrett.—On May 27, 1958, the result of an accident, Ian James Merrett, M.B., B.S., of Wallington, Surrey, aged 24.
Robb.—On March 2, 1958, Duncan Campbell Robb, M.D., of 30, Emerson Avenue, Linthorpe, Middlesbrough, Yorks, aged 52.
Sheeran.—On May 31, 1958, James Henry Callow Sheeran, M.B., B.Ch., of 44, Campbell Road, Bow, London, E.
Slater.—On May 28, 1958, in hospital, Leigh-on-Sea, Essex, Peggy Primrose Slater, M.R.C.S., L.R.C.P.
Sullivan.—On June 3, 1958, at Perth, John Sullivan, M.B., Ch.B., D.P.H.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Sensitivity to Penicillin in Vaccine

Q.—*Is it safe for a penicillin-sensitive person to be vaccinated with poliomyelitis vaccine containing penicillin?*

A.—Perry[1] wrote of all-British vaccine ". . . 100 or 200 units of penicillin per ml. are present in the supernatant fluid of all culture bottles. During inactivation with formalin . . . if any penicillin remains, it is certainly less than 0.5 unit/ml. . . . Even if the remaining half-unit is actively present, it is much too small an amount to cause any sensitization . . . to our knowledge no report has been made of any case of sensitization to the antibiotics." In an answer to a question[2] in the *Journal*, our expert stated: "The amount of antibiotic which is recorded as being present in poliomyelitis vaccine appears . . . to be below that which is likely to cause allergic reactions even in the average acutely sensitive cases, but not in the very exceptional case."

REFERENCES
1 Perry, W. L. M., *Brit. med. J.*, 1956, **1**, 566.
2 "Any Questions?" *ibid.*, 1956, **1**, 1058.

Androstanolone and Weight

Q.—*Is it true, as has been reported in the lay press, that hormone tablets named androstanolone may be given under medical supervision to increase weight in thin people?*

A.—Androstanolone (androstane-17-ol-3-one) is an isomer of androsterone, from which it differs pharmacologically in being a much weaker androgen. Nevertheless, it has a fairly powerful nitrogen anabolic activity and so might be expected to increase protein synthesis and therefore lead to weight gain. This indeed does happen, though not regularly, when it is given in a dose of 25–50 mg. daily to underweight people. Some of the weight gain may be due to fluid retention, but in general only a small proportion is so caused. Some individuals are unduly susceptible to androgens and may develop hirsutism, acne, or, if treatment is continued regardless, deepening of the voice, even with therapeutic doses. It is probably wisest to interrupt treatment after two or three months in any case, resuming it, if necessary, a month or two later.

Most really thin people, excluding, of course, those who are suffering from wasting diseases or are undernourished for reasons outside their own control, have very small appetites. It therefore follows that unless their total calorie intake can be increased substantially, neither androstanolone nor any other agent, unless it stimulates appetite (which androstanolone may do to a limited extent), can have much effect on their weight.

Polyandry and Sterility

Q.—*What evidence is there to support the assertion that polyandry tends to produce sterility?*

A.—From observations in an extensive study of polyandry in Ceylon, India, and Tibet, I would say that there is no relation between polyandry and sterility. I have seen a woman in south-west India, married to three brothers, by whom she had had 18 children. Of course, the spread of venereal diseases through polyandry tends to diminish fertility, but this is incidental to polyandry, not a direct consequence of it. The altitude in Tibet may be a reason for a lesser degree of fertility among its people. Studies in South America have shown, I believe, that the Spaniards in the Andes noted a lessening in the fertility of their immigrants. Some might argue that prostitutes tend to be less fertile. But observation on this count is not very good, and much more study would be necessary before a really serious reply could be given. There is a tendency to underestimate intermediary causes of sterility, such as venereal disease, and to look upon polyandry itself as being a cause of infertility. It is not as simple as that.

Aspirin and Coagulation Rate

Q.—*Do aspirin and calcium aspirin in large or continuous doses have any effect on the coagulation rate?*

A.—Acetylsalicylic acid (aspirin) in very large doses has been shown to produce a haemorrhagic state in experimental animals. This is due to hypoprothrombinaemia, and is preventable by an adequate intake of vitamin K in the diet. Ordinary therapeutic doses of the drug in man can be shown to cause a slight reduction in the prothrombin concentration of the plasma. This may not be detectable by the usual Quick method of estimating prothrombin in undiluted plasma, but a prolongation of the prothrombin time is usually found when diluted plasma is used. There is not always good correlation between the plasma salicylate level and the degree of hypoprothrombinaemia, but, in general, high salicylate levels such as are commonly employed in the treatment of acute rheumatism are usually associated with an appreciable reduction in prothrombin level. The coagulation time of whole blood may be slightly prolonged. In spite of these facts haemorrhagic manifestations are not usually a feature of acute aspirin poisoning, and although there are cases on record where the prolonged administration of salicylates has produced an increased tendency to haemorrhage they are rare. Since prothrombin is formed in the liver it is probably unwise to give aspirin in high or prolonged dosage to patients with known liver disease. The gastro-intestinal bleeding which sometimes follows the use of aspirin is due to gastric irritation rather than to the effect of the drug on the coagulation mechanism.

Histamine-fast Achlorhydria

Q.—*How common is histamine-fast achlorhydria in healthy adolescents and elderly people?*

A.—It has recently been recognized that a test meal using 0.5 mg. of histamine as stimulant, a tube passed without radiological control, and Töpfer's reagent to detect free acid gives a false measure of the frequency of achlorhydria. Using 0.04 mg. per kg. body weight of histamine after a preliminary injection of mepyramine, a radio-opaque tube with its tip in the pyloric antrum, continuous gastric suction during the test, and electrometric measurement of the *p*H of the gastric juice, some free acid can be detected in the juice of all normal subjects at all ages.[1 2] Töpfer's reagent changes colour at *p*H 3.5. Studies on patients with pernicious anaemia suggest that hydrochloric acid is present if the gastric juice is more acid than *p*H 5.

REFERENCES
1 Kay, A. W., *Brit. med. J.*, 1953, **2**, 77.
2 Card, W. I., and Sircus, W., *Modern Trends in Gastro-enterology*, 1958, p. 180. Butterworth, London.

Recurrence of Influenza Epidemics

Q.—*Does last winter's influenza epidemic make a further epidemic this year or next year more or less likely than it would otherwise be?*

A.—In general, influenza A usually skips a year between epidemics. However, the Asian virus has already behaved as a most successful and unusual parasite. This could mean that it has saturated sufficient members of the population this winter to prevent a recrudescence for two years. On the other hand, probably 50% of the population will be susceptible to the Asian antigen by next winter, and no one knows whether this is enough to permit a conflagration again or not. Probably the balance of evidence favours a recrudescence in 1958, though on a lesser scale than 1957. It seems unlikely that a variant virus with greater pneumotrophic properties than the Asian virus will arise, but the possibility remains. The evidence which suggests that one

influenza epidemic leads to a second one within a relatively short period is the second and third waves of the 1918 pandemic, which followed at a few months' interval, and the second and third waves which followed the 1889 pandemic at twelve-months intervals. As the cause of the various waves of both pandemics remains unknown, but could have been entirely different agents, it seems unwise to use these epidemics as a basis for prediction. However, influenza B has not caused a widespread epidemic for several years, though there were minor outbreaks in 1954–5. It is not at all unlikely, therefore, that either the Asian virus or influenza B or both viruses will cause outbreaks next winter.

Danger from Fruit Spraying

Q.—*What danger is there to people living close to orchards where arsenic and mercury mist sprays are used on the fruit trees?*

A.—The danger from the drift of toxic sprays can only be determined by measuring the deposit formed on exposed crops. The public analyst could estimate the arsenic or mercury content of contaminated vegetation, but methods are not always generally available for some of the newly developed pesticides. Though any contamination is undesirable and, if serious, is an indication of poor spraying practice, the actual danger of poisoning is very small. Except in a high wind (when spraying should not be done), only the finest particles will drift, and these carry the smallest quantity of toxic material. The quantities in the actual spraying solution are fairly critical, for if gross excess is used the sprayed trees will be damaged. Furthermore, much of any deposited material would be removed when the vegetables were washed before cooking or eating.

Climate

Q.—*What is meant by the words "relaxing" and "stimulating" as applied to the local atmosphere of, say, a seaside resort?*

A.—It is impossible to define the words "relaxing" and "stimulating" as usually applied to climate. Probably the qualities described mainly refer to the temperature and air movement. If the climate is said to be "stimulating" or "bracing" it is almost certainly moderately cold, so that one must take physical exercise to keep warm. In a "relaxing" climate it is frequently warm enough to enable visitors to sit in a deck chair in comfort. There have been many investigations made in attempts to discover some peculiar quality of climate, such as variations in percentage of ozone, but so far the results of such inquiries have not been fruitful.

"Wind"

Q.—*What are the gases responsible for "wind" in the intestines and what is their origin?*

A.—The sensation of "wind" in the abdomen is not always due to the presence of gas in the intestines. Gases commonly present are carbon dioxide, 9–25%; oxygen, 0–6%; methane, 0–30%; hydrogen, 0–44%; hydrogen sulphide, trace[1]; nitrogen, remainder.[2 3] These gases are present from swallowing (O_2 and N_2); diffusion from the blood through the intestinal wall (CO_2 and O_2); or fermentation in the intestinal lumen (H_2, CH_4, and CO_2). It is usually impossible to say which of these factors produces the most gas, but swallowing is responsible for much of it. Gases are lost by eructation, by the passage of flatus, and into the blood stream by diffusion. The average quantity of gas in the digestive tract is one litre[4] and between 500 and 2,000 ml. of gas are passed as flatus daily.[1]

Beans and other legumes will produce an increase of flatus in many people and cabbage may do the same.[1] The reason for this is unknown, but it must be borne in mind that the commonest cause of increased flatus is intestinal hurry, which leaves less time for gases to be absorbed by diffusion. Dry "activated" charcoal can absorb large quantities of gases, particularly heavy ones with large molecules. However, this property is greatly reduced when the charcoal is wet and mixed with electrolytes and colloids, as in the gut. Indeed, it is probable that charcoal can absorb little of any kind of gas in the intestine.[5 6]

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2. Fries, J. A., *Amer. J. Physiol.*, 1906, **16**, 468.
3. Askevold, F., *Scand. J. clin. Lab. Invest.*, 1956, **8**, 87.
4. Blair, H. A., Dern, R. J., and Bates, P. L., *Amer. J. Physiol.*, 1947, **149**, 688.
5. Emery, E. S., *J. Amer. med. Ass.*, 1937, **108**, 202.
6. Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1955, p. 1020. Macmillan, New York.

Animal Sera

Q.—*Are sera for passive immunization always made from horse serum, or is other animal serum sometimes used to minimize the risk of anaphylaxis?*

A.—Antitoxic and antibacterial sera for passive immunization are usually made from horse serum because of the large yield and because the antibody response of the horse to a variety of antigens is good. Very occasionally rabbit sera have been prepared—for example, pneumococcal antiserum (which is no longer needed) and pertussis antiserum (which is seldom if ever used now). As Moynihan[1] has shown, however, the risk of serious consequences, such as anaphylaxis, following the administration of the present highly purified sera is very small, and even the serum sickness and local reaction rates together are not more than about 5%.

REFERENCE

1. Moynihan, N. H., *Brit. med. J.*, 1956, **1**, 260.

NOTES AND COMMENTS

Medicines on Holiday.—Dr. CYRUS IVE (Epsom) writes: In answer to this question ("Any Questions?" May 31, p. 1313) your expert writes: "T.A.B. inoculations are unnecessary (they may be advisable for those who propose to visit Spain or Southern Italy)." I have analysed the cases of enteric fever which were detected in Continental holidaymakers in 1957, in an area of Surrey with a population of 150,000. The number of Continental travellers from this total is unknown. Four cases were reported, two of whom contracted their infection in France (1 typhoid and 1 paratyphoid) and two in Italy (both paratyphoid). Spain did not contribute cases in 1957, but did so in previous years. On this evidence it would seem that travellers to France should be given the same advice as those to Spain and to Italy. Two of the persons concerned were members of organized student groups, and a third was abroad under a "student exchange" system. I would suggest that the necessity for T.A.B. inoculation should be given careful consideration for members of student groups travelling in southern European countries, including France. Admittedly the figures given above are small, but I have noted a regular incidence of enteric fever in these circumstances for several years past.

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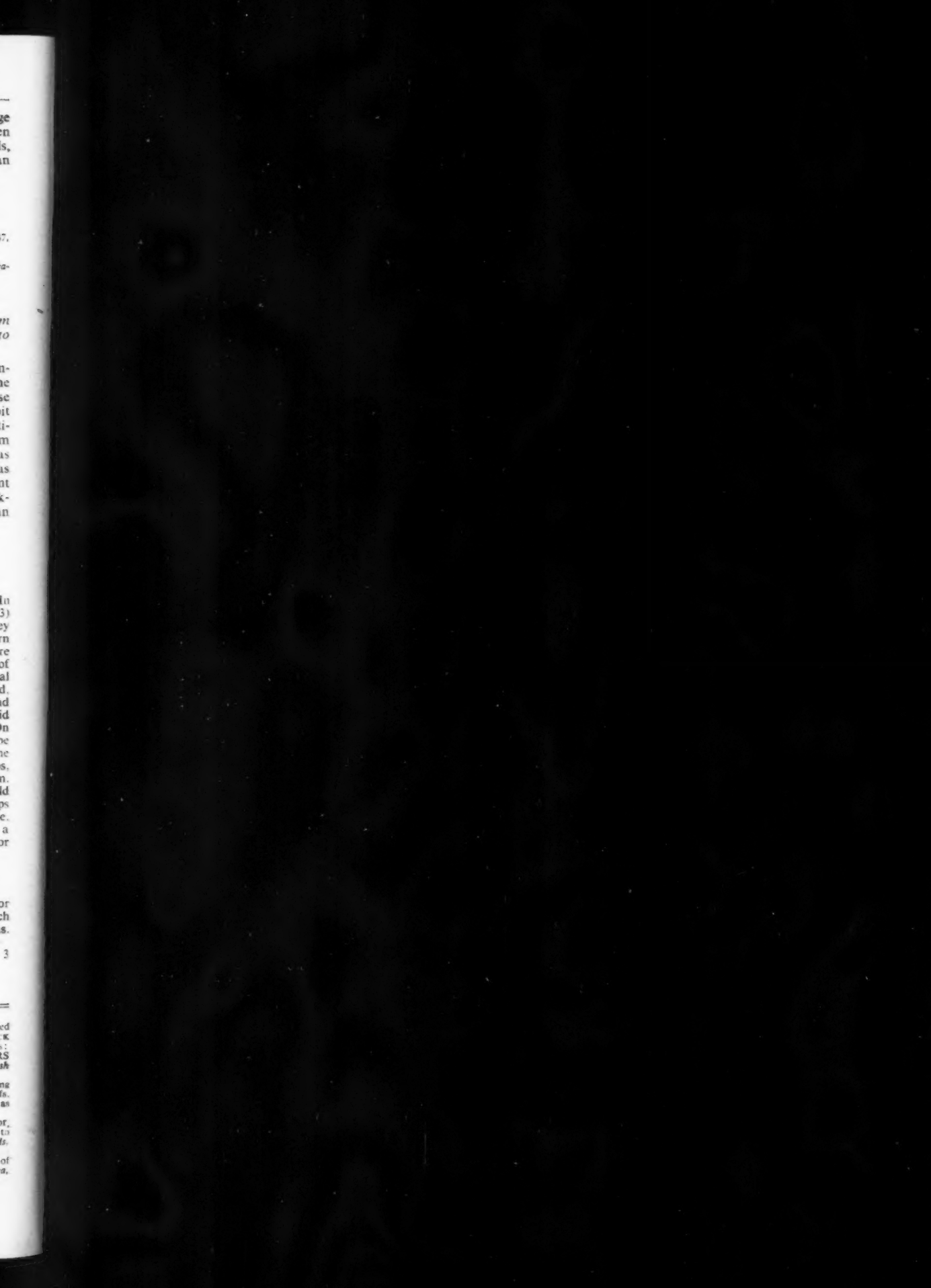
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